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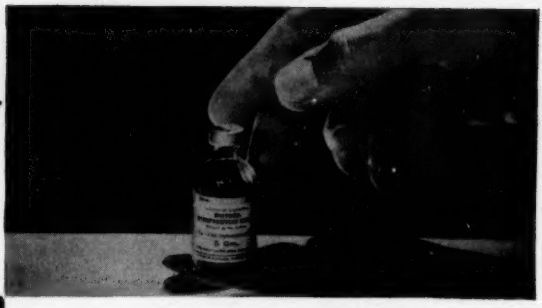

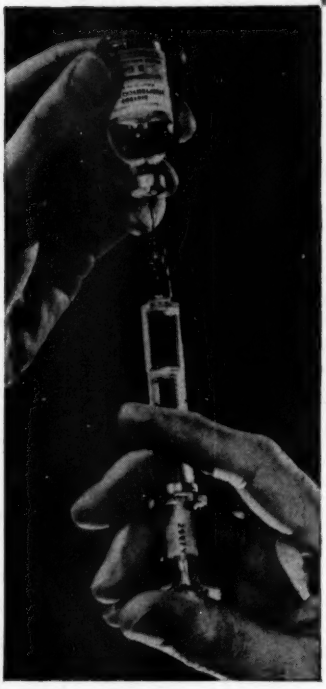

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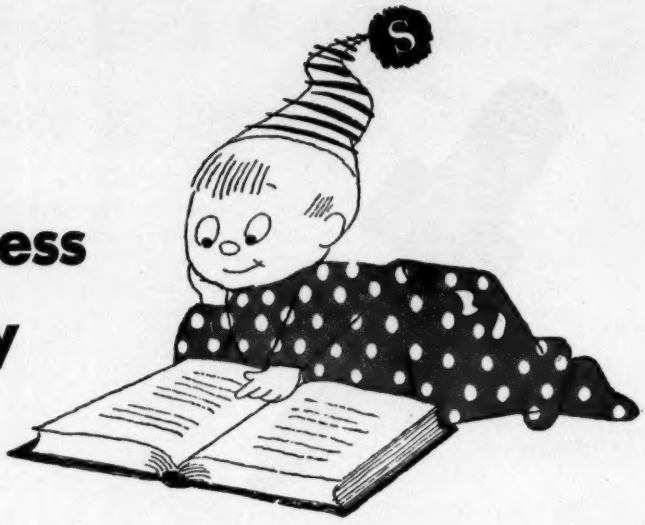

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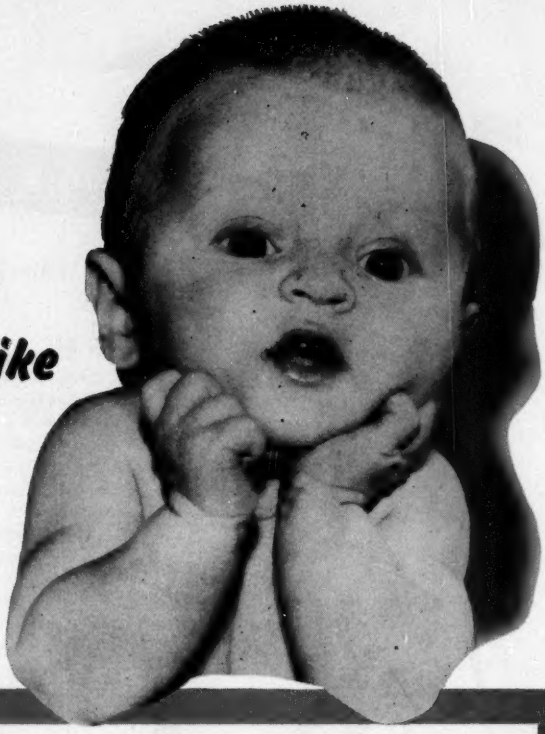

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# EFFECT OF CORTISONE AND CORTICOTROPIN (ACTH) ON THE ACUTE PHASE OF RHEUMATIC FEVER

## Further Observations

ARLIE R. BARNES, M.D.
HARRY L. SMITH, M.D.
CHARLES H. SLOCUMB, M.D.
HOWARD F. POLLEY, M.D.
AND
PHILIP S. HENCH, M.D.
ROCHESTER, MINN.

IT IS widely known that rheumatic fever and rheumatoid arthritis produce marked reactions in the collagen tissues of the body. The evidence that cortisone (compound E; 17-hydroxy-11-dehydrocorticosterone) and corticotropin (ACTH; pituitary adrenocorticotropic hormone) were effective in suppressing the disabling reactions in tissues of patients with rheumatoid arthritis suggested at once that the effects of these hormones on the course of rheumatic fever should be investigated. Accordingly, some of us first administered cortisone to a patient with rheumatic fever on March 28, 1949 (Case 1 of this report), and corticotropin to another patient with this disease on May 14, 1949 (Case 4 of this report). In the preliminary report[1] of May 25, 1949, it was stated that administration of cortisone during the acute phase of rheumatic fever was attended by rapid disappearance of the following conditions: fever, tachycardia, polyarthritis, elevated sedimentation rates (Westergren method) and abnormal electrocardiographic changes. At the time of that report, a patient with rheumatic fever had received injections of corticotropin for a period of 11 days, and it was recorded that the response of the patient appeared to parallel entirely the effects observed in cases in which cortisone had been administered. Cases 1, 2 and 3 of the cited preliminary report[1] are respectively cases 1, 10 and 2 of this article.

In studying the effect of any agent on the course of a self-limiting disease such as rheumatic fever, one must take into account the stage in the course of the disease

From the Division of Medicine, Mayo Clinic.

Read before the Section on Pediatrics at the 99th Annual Session of the American Medical Association, San Francisco, June 29, 1950.

The cortisone used in this study was provided by Merck & Company, Inc., Dr. Randolph Major, Vice President, and Dr. James Carlisle, Medical Director. Armour and Company, Dr. John R. Mote, Director of Research, supplied the corticotropin (ACTH; pituitary adrenocorticotropic hormone).

1. Hench, P. S.; Slocumb, C. H.; Barnes, A. R.; Smith, H. L.; Polley, H. F., and Kendall, E. C.: The Effects of the Adrenal Cortical Hormone 17-Hydroxy-11-Dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:277-297 (May 25) 1949.

at which the agent is administered. In rheumatic fever the results of administering any effective agent will vary according to whether it is given to a patient early in the first attack of rheumatic fever or to a patient who has had previous attacks of the disease complicated by valvular injury or cardiac enlargement or both. Similarly, the results in acute rheumatic fever may vary, depending on the presence or absence of rheumatic carditis or of congestive heart failure.

For purposes of analysis of the effects of cortisone and corticotropin on acute rheumatic fever, our patients can be classified in the following categories:

1. Those with acute rheumatic fever in the first attack and without previous damage to the heart valves or carditis (8 cases).

2. Those with acute rheumatic fever in the first attack, without previous valvular damage, but complicated by rheumatic carditis (2 cases).

3. Those with acute rheumatic fever in a recurrent attack, with or without evidence of previous damage to the heart valves, and with or without probable previous carditis (4 cases).

### ACUTE RHEUMATIC FEVER IN THE FIRST ATTACK AND WITHOUT PREVIOUS DAMAGE TO THE HEART VALVES OR CARDITIS

CASE 1.—*History.*—A girl, 15 yr. of age, was admitted to the hospital on March 26, 1949. She gave no history of arthritis, growing pains or chorea, and no member of her family had had rheumatic fever. Her previous diseases of childhood had included scarlatina at 6 yr. of age.

Her present illness had begun March 8, with headache, generalized aching, weakness, sore throat, and nausea. The illness had lasted four days and had been called "flu."

On March 23, she had felt unusually tired and "achy," and the next day her heels had been red and tender and her wrists, elbows, and back had become stiff and sore. On March 25, her ankles had become tender, hot, and swollen, and her temperature had been 101.5 F. She was brought to the hospital the next day because she was unable to get out of bed. The patient had lost 5 lb. (2.3 kg.) within three weeks.

*Examination.*—The ankles were moderately swollen, warm, tender (grade 2), and painful on motion; also, the left elbow and right knee were very tender. The temperature was 100.6 F., pulse rate 112 per minute, and blood pressure 126 mm. of mercury systolic and 80 diastolic. The heart was not enlarged; murmurs were not heard, but the first and second heart sounds were poorly differentiated. A diagnosis of acute rheumatic fever was made.

The day that administration of cortisone was started, the patient's temperature was 101.8 F., the sedimentation rate was 114 mm. (Westergren method), the P-R interval was 0.24 sec., the heart rate was 112 beats per minute, and the ankles and knees were so painful that voluntary motion was impossible and passive motion was unbearable.

*Use of Cortisone.*—At 7 p. m. on March 28, the first injection of 100 mg. of cortisone was given. This and subsequent injections are recorded in Figure 1. A total of 4.65 gm. of cortisone was administered in the course of 38 days.

*Effects Observed After Use of Cortisone.*—After cortisone was first administered, polyarthritis disappeared in three and one-half days. Changes in temperature, heart rate, P-R interval, and sedimentation rate are shown in the graph just mentioned (Fig. 1). The albumin-globulin ratio rose from an initial value of 1.14:1 to 1.7:1 five days before administration of cortisone was discontinued. The values for albumin rose, and that for globulin fell. The concentration of hemoglobin was 11.6 gm. per 100 cc. four days after cortisone first was given and 14.4 gm. twenty-two days later. After the menstrual flow which started April 18, 1949, menses ceased.

On May 6 a diagnosis of infectious mononucleosis was made. This diagnosis was based on the presence of a local epidemic of this disease, a decreased polymorphonuclear leukocyte count, lymphocytosis (83%), mild adenopathy, presence of heterophile antibodies (titer 1:7,168), mild splenomegaly, and a characteristic cellular reaction discernible in material obtained by

sternal puncture. The mononucleosis was held responsible for the slight increase in the sedimentation rate, which varied between 37 and 23 mm. (April 22 to May 10).

*Reappearance of Symptoms After Use of Cortisone Ceased.*—After May 20, a rise in the sedimentation rate, a parallel rise in the pulse rate, and an increase of the P-R interval to 0.20 sec. on June 6 indicated a flare of the active rheumatic state. Recurrence of joint symptoms did not accompany this flare. Without further use of cortisone these values declined to normal by June 29 (Fig. 1). The patient was dismissed from the hospital on July 2, 1949.

*Murmurs.*—The murmurs observed in this case were variable and intermittent. A short, soft diastolic murmur to the left of the sternum was heard April 13. It was present intermittently after that until June 17. Inconstant systolic murmurs of variable character were heard at the base and apex of the heart. However, at the time of dismissal no murmurs were heard in the heart.

*Follow-Up.*—The patient was re-examined April 6, 1950, nine months after she had been dismissed from the hospital. She had resumed the active life of a schoolgirl in September, 1949. Examinations disclosed no cardiac murmurs, and a teleroentgenogram revealed that the heart

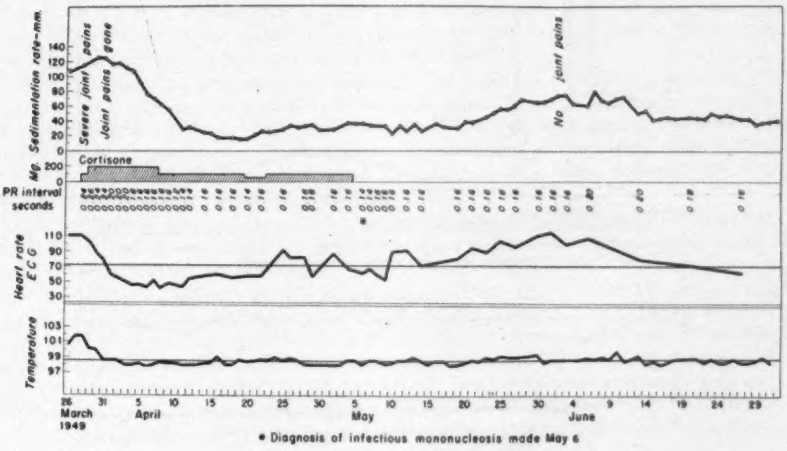


Fig. 1 (Case 1).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

was normal in size and contour. A scanty menstrual flow occurred July 17, and thereafter the patient resumed her previous menstrual pattern.

CASE 2.—*History.*—A boy, 17 yr. of age, was admitted to the hospital on April 16, 1949. He had had scarlatina at 4 yr. of age and pain in the knees at the age of 12 yr. but gave no history of chorea or rheumatic fever. He was told that he had had leakage of the heart when he was 12 yr. old; however, at 16 yr. of age he had been told that his heart was normal.

On March 10, 1949, a persistent cold and cough had begun. Between April 1 and 5, the patient had had tonsillitis, which had been relieved by one injection of penicillin. Febrile polyarthritis had begun on April 9; taking of 80 grains (5.2 gm.) of acetylsalicylic acid daily relieved this only partially.

*Examination.*—The patient was acutely ill on admission. Several joints were red, swollen, and tender. The temperature and pulse rate rose rapidly (Fig. 2). The blood pressure was 110 mm. of mercury systolic and 50 diastolic. The heart was considered to be of normal size. The second pulmonic sound was markedly accentuated, and the first sound at the apex was loud. A systolic apical murmur of marked intensity was heard and was well transmitted to the left axilla.

*Use of Cortisone.*—Administration of cortisone was begun on April 21; 200 mg. was given at 8 p. m. Doses given thereafter are represented in the graph (Fig. 2). A total of 3.45 gm. was administered in twenty-two days.

*Effects Observed After Use of Cortisone.*—Polyarthritis had practically disappeared by the third day after the first injection of cortisone (slight tenderness of the metatarsal joints persisted until May 2). The temperature returned to normal in 24 hours; the heart rate, which already was slow, dropped still further, and bradycardia persisted for about two weeks; the P-R interval fluctuated slightly while the patient was receiving cortisone, and it was not considered that the value 0.16 sec. was abnormal (Fig. 2). The albumin-globulin ratio rose from 1.06:1 on April 22 to 1.9:1 on May 5. This rise was accounted for partly by increase in the concentration of serum albumin but chiefly by decrease in the globulin factor. The values for hemoglobin did not change significantly. After use of cortisone had been discontinued there was a mild recurrence of two features of acute rheumatic fever; these consisted of increase in the

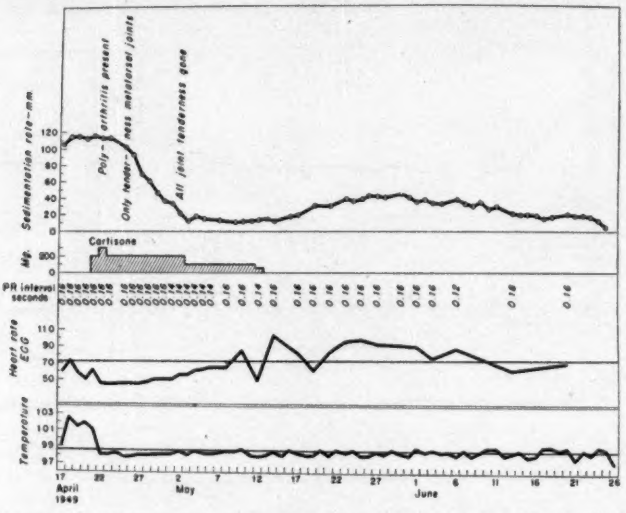


Fig. 2 (Case 2).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

sedimentation and heart rates, but articular and muscle pain was absent. The increases mentioned, gradually returned to normal without further use of cortisone.

*Murmurs.*—A systolic apical murmur noted on the initial examination persisted essentially unchanged throughout the patient's stay in the hospital. From May 19 to June 21 a diastolic murmur was heard to the left of the sternum but was not present at the time of the patient's dismissal. The patient was dismissed from the hospital in good general condition June 26, 1949.

*Follow-Up.*—The patient was examined approximately 10 mo. later. He had had several colds in the course of the winter and had one at the time of this examination. His temperature was 99.0 F., the sedimentation rate 44 mm., and the P-R interval 0.16 sec. No cardiac murmur could be heard at this examination, and a teleroentgenogram revealed that the heart was of normal size and contour. He was readmitted to the hospital May 23, 1950, in a recurrent attack of acute rheumatic fever, for which he again was receiving cortisone as this report was being written.

CASE 3.—*History.*—A boy, 6 yr. of age, was admitted to the hospital on March 30, 1950. He never had had rheumatic fever, but episodes of tonsillitis and otitis media had occurred in the past few years.

Three weeks before his admission the patient had had a temperature of 102 F. in association with earache. Three days following two injections of procaine penicillin G (duracillin®), the temperature had returned to normal and the patient had felt well for about a week. Penicillin and aureomycin had been given for recurrent fever accompanied by spontaneous epistaxis. The symptoms had subsided again, and the patient had returned to school for one week.

The patient first had complained of pain in the left metatarsal region six days before admission. Migratory polyarthritis and episodes of epistaxis had followed. At the time of admission, the patient complained of pain in the extremities, the inguinal regions, the left metatarsal joints, and the heels.

*Examination.*—The child was slender and appeared pale; the skin was hot and dry. Because of severe pain the patient could not turn in bed or tolerate movements of the legs. His temperature was 101 F., pulse rate 104 beats per minute, and blood pressure 96 mm. of mercury systolic and 50 diastolic. Soft systolic, pulmonic, and apical murmurs were present and were graded 2. The diagnosis was acute rheumatic fever.

*Use of Cortisone.*—Administration of cortisone was begun on March 31. The dosage was as follows: 100 mg. March 31; 100 mg. daily from April 1 to 4, inclusive; 75 mg. on April 5; 50 mg. April 6 to 9, inclusive; 25 mg. April 10 to 23, inclusive; none was given April 24 or 26, but 25 mg. was given April 25 and 27; none was given thereafter. A total of 1.175 gm. of cortisone was administered in an over-all period of 28 days.

After administration of cortisone had been begun, the temperature returned to normal in 24 hours, the pulse rate dropped from 98 to 62 beats per minute in seven days, and articular pain disappeared largely in 24 hours and completely in three days. The sedimentation rate decreased from 121 to 21 mm. in 13 days. The P-R interval decreased from 0.14 to 0.12 sec. in three days. The albumin-globulin ratio rose from 1.2:1 to 2:1 in 22 days owing predominantly to a decrease in the value for serum globulin.

The patient was dismissed from the hospital on April 29, 1950. His general condition was good, and he had gained 5¾ lb. (2.6 kg.) during his stay in the hospital. A barely audible systolic murmur was present at the apex.

*Follow-Up.*—The patient was re-examined May 27, 1950. He felt well, but walking had not been permitted in the intervening month. His parents reported that he had had a temperature of 99.2 F. on three days, but otherwise the temperature had remained normal. They had observed a pulse rate of 100 to 102 beats per minute when the patient was awake but reported that the rate was much slower when he was asleep. The sedimentation rate was 7 mm. and the P-R interval 0.12 sec. A very faint apical systolic murmur was heard but without significant transmission. The teleroentgenogram indicated that the heart was normal in size and contour.

CASE 4.—*History.*—A boy, 14 yr. of age, was admitted to the hospital May 11, 1949, in his first attack of rheumatic fever. He gave no history of previous chorea, growing pains, or articular symptoms.

Early in April, 1949, a sore throat, accompanied by a temperature of 104 F., had developed. Sulfonamides and penicillin had been given, and this illness had subsided in three days. In the five days before admission polyarthritis had developed, at which time the temperature had risen to a maximum of 101 F.

*Examination.*—The knees and the left wrist were slightly swollen; the left wrist was very tender. The pulse was regular. The blood pressure was 114 mm. of mercury systolic and 60 diastolic. The maximal temperature in the three days before the administration of corticotropin was begun was 102.4 F. The apex beat of the heart was just below and within the area of the nipple. A soft, blowing, systolic murmur was heard at the apex and to the left of the sternum, with maximal intensity in the latter area; it was not transmitted outside the region of the apex.

*Use of Corticotropin.*—On May 14 and 15, 25 mg. of corticotropin was administered intragluteally. The dosage thereafter was 18 mg. daily from May 16 to 25, inclusive; 20 mg. daily for three days (May 26 to 28), and 15 mg. daily for eight days (May 29 to June 5), a total of 410 mg. in 23 days (Fig. 3).

Improvement in the patient's condition after administration of corticotropin had been begun was evidenced by decreases in articular pain, temperature, heart rate, P-R interval, and sedimentation rate; these are represented in the cited graph (Fig. 3). The concentration of hemoglobin rose from a primary value of 11.3 to 12.9 gm. per 100 cc. of blood in 10 days. The albumin-globulin ratio increased from 1.2:1 to 1.7:1 in 21 days. This involved a substantial drop in the globulin fraction and an increase in the serum albumin component.

*Flare (Reappearance)*[2] *of Certain Manifestations of Acute Rheumatic Fever.*—After the administration of corticotropin had been discontinued, June 6, the sedimentation rate rose gradually; simultaneously, the P-R interval increased and the apical heart rate, which was slow during the use of corticotropin, rose moderately (Fig. 3). During this time there was no recurrence of articular symptoms and no marked change in the albumin-globulin ratio. The value for hemoglobin decreased from 14.4 gm. per 100 cc. of blood to 11.3 gm. on June 28.

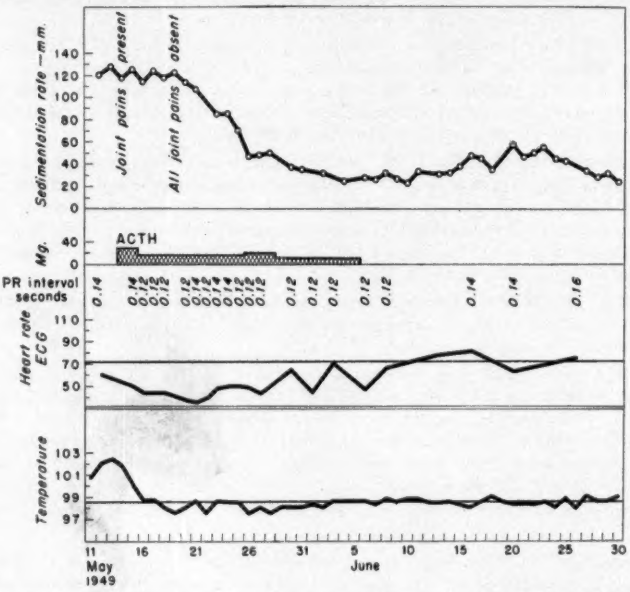


Fig. 3 (Case 4).—Effect of corticotropin on temperature, pulse rate, sedimentation rate, and P-R interval.

The patient was in good general condition at the time of his dismissal from the hospital July 1, 1949. The cardiac murmurs previously described were still present at the time of dismissal.

*Follow-Up.*—The patient was last examined 10 months after his dismissal from the hospital. He was in excellent physical condition; no cardiac murmurs were heard, and the heart was not enlarged.

2. The term "flare" (or "reappearance") as used in this paper, refers to the reappearance of some or all of the acute manifestations of rheumatic fever, in the current attacks. See the section headed "Flares of Acute Rheumatic Fever After Withdrawal of Cortisone or Corticotropin."

The term "recurrence" indicates a new attack of acute rheumatic fever affecting a patient who has recovered from a previous acute attack of the disease.

The term "persistence" means that the patient never completely recovered from acute rheumatic fever; while the condition persists, a flare may or may not be observed.

CASE 5.—*History.*—A married woman, 24 yr. of age, was admitted to the hospital March 21, 1950, complaining of slight pain in the right knee. There was no previous personal or family history of rheumatic fever. She always had enjoyed good general health until about three weeks before admission, when she had a severely sore throat. Slightly more than two weeks before admission and in the succeeding days, polyarthritis developed.

*Examination.*—The patient was well developed and moderately obese. The heart rate is represented in Figure 4; the rhythm was regular. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. A soft systolic murmur was heard over the entire precordium, maximally at the apex; it was not transmitted to the axilla.

*Subsequent Observations Prior to Use of Cortisone.*—Maximal elevations of temperature occurred on March 25, 26 and 27. A pericardial friction rub was heard March 25 and 26 but not thereafter. On March 26, there was tenderness, graded 3, of numerous joints.

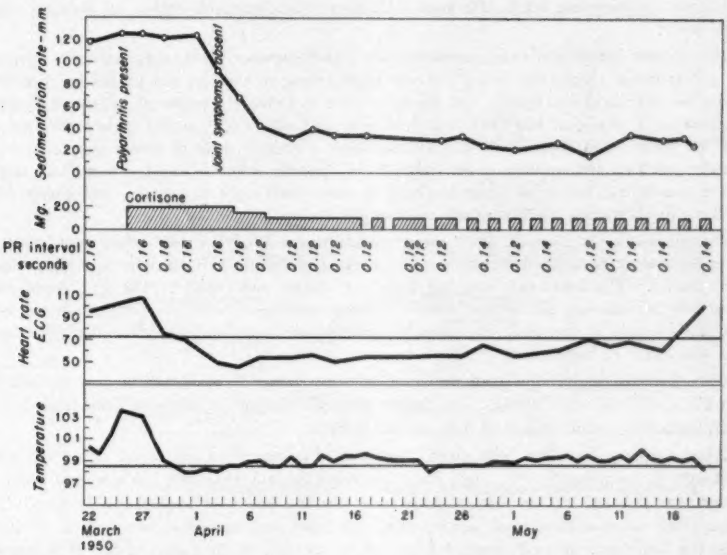


Fig. 4 (Case 5).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

*Use of Cortisone.*—Intramuscular administration of 200 mg. of cortisone was begun on March 26, 1950 (Fig. 4). A total of 5.15 gm. was given within 55 days (March 26 to May 19). An additional 300 mg. was given between May 19 and 24, as is described below.

After the administration of cortisone had been begun, articular pain and tenderness soon disappeared and the heart rate rapidly became normal. Thereafter, bradycardia was present for nearly four weeks, during which time the heart rate did not exceed 56 beats per minute and the sedimentation rate decreased (Fig. 4). The concentration of hemoglobin rose from 11.2 to 12.8 gm. per 100 cc. of blood in 10 days, and the number of leukocytes decreased from 15,500 to 6,100 per cubic millimeter of blood in nine days. A pericardial friction rub was heard only on March 25 and 26.

*Follow-Up.*—The patient was dismissed from the hospital May 19, 1950, with provision for her to receive 100 mg. of cortisone on alternate days, until it could be established that the acute rheumatic state had terminated. No cardiac murmurs were heard at the time of dismissal. She was directed to report weekly for observation. On this program the patient received her last injection of cortisone on May 24, 1950.

She was last examined July 7, 1950. The sedimentation rate was 38 mm. The patient felt well. No murmurs were heard, and the heart was not enlarged.

*Comment.*—It is believed that the plan of prolonged administration of cortisone on a reduced or intermittent dosage, such as was employed in this case (Fig. 4), is preferable to the method used in many of our cases. The persistence of a sedimentation rate of 38 mm. six weeks after the last injection of cortisone indicates that the rheumatic state continued well beyond this period of prolonged administration of cortisone. If its administration had been discontinued after one month, we would have anticipated from our experience in other cases a sharp reappearance of the acute manifestations of rheumatic fever.

CASE 6.—*History.*—A boy, 14 yr. of age, was admitted to the hospital Nov. 27, 1949, in his first attack of rheumatic fever. He gave no history of scarlet fever, chorea, or previous rheumatic fever.

His present illness had begun insidiously in mid-September, 1949, with lassitude, dyspnea, and polyarthritis. Vomiting, fever, and continued aching in the feet and ankles had occurred during the first week in October. In the latter part of October, because of increasing dyspnea on exertion, a physician had been consulted, who had placed the patient in bed; the patient then felt better. On Nov. 22, 1949, there had been a sudden onset of severe pain in the left shoulder and pain and swelling in the right elbow. Shortly prior to his admission to the hospital the patient had had to sit up in bed once or twice each night to breathe comfortably. He had been given sodium salicylate daily for five days before admission.

*Examination.*—On Nov. 28, 1949, the temperature was 101.5 F.; mild pallor was observed, but subcutaneous nodules could not be felt. Movements of the left shoulder and right elbow were painful. The heart rate was 112 beats per minute and regular. The second pulmonic sound was accentuated, and a loud systolic murmur was heard over the precordium but with maximal intensity at the apex. No diastolic murmur was heard at this time, but a third heart tone was heard in middiastole.

*Use of Cortisone.*—Administration of cortisone was started Nov. 30, and on that day and the next the daily dose was 200 mg. The patient received 100 mg. of cortisone daily from Dec. 2 to 29, inclusive, a total dosage of 3.20 gm. in 30 days.

After cortisone first had been given, joint pain disappeared in two days. However, after eight days it was noted that the right elbow could not be fully extended, but a normal range of motion was restored to this joint after physical therapy had been applied for 11 days. The temperature returned to normal in four days, the heart rate decreased from 112 to 75 in 12 days, the sedimentation rate dropped from 120 to 20 mm. in 20 days and the P-R interval decreased from 0.22 to 0.16 second in eight days. The hemoglobin increased from an initial value of 11.4 gm. per 100 cc. of blood two days before use of cortisone had been started to 13.4 gm. 14 days after it was first administered. The albumin-globulin ratio rose from 1.08:1 to 2:1 in 21 days, partially owing to increase in the albumin fraction but chiefly owing to decrease in the globulin component.

*Murmurs.*—A short diastolic murmur was heard intermittently during the first few days after the patient received cortisone but never was heard thereafter until rheumatic fever recurred. A loud systolic murmur was heard at the initial examination. The history indicated that the onset of rheumatic fever antedated the use of cortisone, possibly as long as six weeks. It was suspected that this murmur indicated that acute or subacute valvulitis existed at the time of admission. It was of unusual interest to observe whether use of cortisone would reverse this inflammatory process either shortly or ultimately. It should be recorded that the character of this murmur did not change while the patient was in the hospital.

The patient was dismissed from the hospital in good general condition on Dec. 30, 1949.

*Follow-Up.*—The first re-examination was made Jan. 7, 1950. The systolic, apical murmur was present and essentially unchanged. The heart was not enlarged. The P-R interval was 0.14 sec. and the sedimentation rate was 22 mm.

The second re-examination prior to the onset of recurrent, acute rheumatic fever was made March 4, 1950. The patient was feeling well and was walking 10 blocks each day. The cardiac findings were unchanged from those of his last previous examination. At this visit the sedimentation rate was 34 mm. There were no joint pains.

On March 16, 1950, he had contracted a cold and a diagnosis of influenza had been made, for which his physician had kept him in bed for two weeks. He again reported at the Mayo Clinic for examination April 24, 1950. He now had carditis with marked cardiac enlargement, systolic and diastolic murmurs at the apex and a sedimentation rate of 40 mm. He was returned to his home for rest in bed under the care of his home physician.

The last re-examination was made May 22, 1950. The murmurs were unchanged from the last previous visit. The heart still was enlarged, but its transverse diameter was 2.5 cm. less than at the last visit.

*Comment.*—The sequence of events in this case illustrates the necessity of frequent observation of these patients after administration of cortisone has been

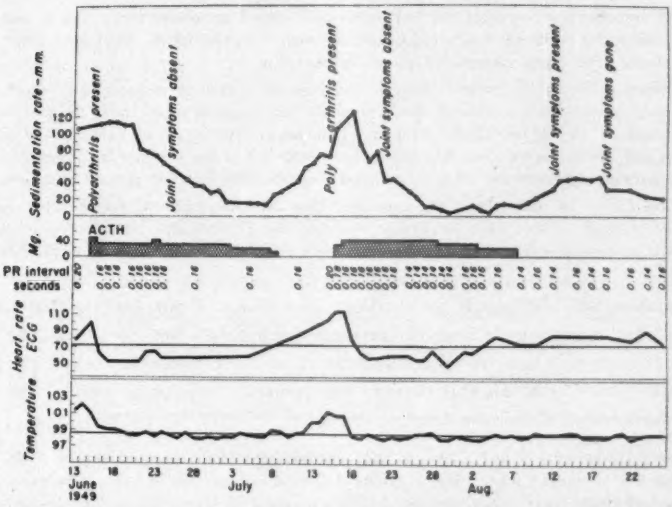


Fig. 5 (Case 7).—Effect of corticotropin on temperature, pulse rate, sedimentation rate, and P-R interval.

discontinued. Whether the reappearance of certain manifestations of acute rheumatic fever indicated persistence of the initial rheumatic state or a recurrent attack of rheumatic fever, it would have been advantageous if the situation could have been recognized promptly. Then injections of cortisone could have been resumed.

CASE 7.—*History.*—A youth, 18 yr. of age, was admitted to the hospital June 11, 1949, in his first attack of rheumatic fever. Except for repeated attacks of tonsillitis, he had had no previous illness.

On May 11, 1949, the patient had become ill with tonsillitis; penicillin had been given, and recovery had occurred in five days. On May 30, polyarthritis had occurred and the temperature had risen to a maximum of 102 F. The polyarthritis had disappeared June 8, after treatment with penicillin and sulfonamides. On June 10, stiffness of the right knee and ankles had recurred.

*Examination.*—The patient was well developed and well nourished. Tenderness to pressure and increased warmth were noted over numerous joints. The maximal elevation of tempera-

ture before administration of corticotropin had been started was 102 F. The pulse was regular and its rate 90 per minute when the patient was sitting up. The blood pressure was 98 mm. of mercury systolic and 60 diastolic. A faint systolic murmur was heard over the base of the heart and at the apex.

*Use of Corticotropin.*—The patient received 45 mg. of corticotropin on June 15 and subsequent amounts corresponding with those represented in Figure 5, a total of 675 mg. in twenty-four days.

After the administration of corticotropin had been started, the temperature returned rapidly to normal, joint manifestations disappeared, and the heart rate, the P-R interval, and the sedimentation rate decreased (Fig. 5). The injections were attended by a rise in the albumin-globulin ratio from 1:1 to 1.5:1 in 24 days. This was accounted for chiefly by a fall in the value for globulin.

Shortly after administration of corticotropin had been discontinued, all the previous manifestations of acute rheumatic fever reappeared. Corticotropin again was administered, a total of 760 mg. being given in 23 days (July 16 to Aug. 7 inclusive). Again the acute manifestations of rheumatic fever were promptly suppressed (Fig. 5).

After injections of corticotropin had been discontinued a second time, certain manifestations of the active rheumatic state reappeared, although in milder form. Without further use of the hormone these signs disappeared in two weeks (Fig. 5).

*Murmurs.*—During the patient's stay in the hospital a systolic murmur was heard rather consistently, sometimes maximal at the base of the heart and at other times most pronounced at the apex or to the left of the sternum. On one or two occasions early in the patient's illness a soft, short, diastolic murmur was heard to the left of the sternum but never thereafter.

The patient was dismissed from the hospital Aug. 27, 1949, in good general condition.

*Follow-Up.*—The patient was last examined May 20, 1950, nine months after his dismissal from the hospital. There were no cardiac murmurs and a teleroentgenogram revealed that the heart was of normal size and contour. The patient was doing heavy physical work without ill effects.

*Comment.*—This case is an excellent illustration of our concept that corticotropin (and the same is true of cortisone) suppresses but does not cure acute rheumatic fever. Omission of administration of these hormones before the active rheumatic state is at an end permits recurrence of one or several of the acute manifestations of rheumatic fever.

CASE 8.—*History.*—A girl, 13 yr. of age, was admitted to the hospital June 6, 1949, in her first attack of rheumatic fever. Her previous childhood diseases had included measles, pertussis, mumps, and chickenpox. There was no previous personal or family history of rheumatic fever.

A severely sore throat and an acute respiratory infection had occurred almost four weeks before the patient's admission, but these had subsided in three days. In the 10 days prior to her admission to the hospital anorexia had developed, together with a temperature ranging from 101 to 102 F. and migratory polyarthritis.

*Examination.*—The patient was well nourished and well developed. The left knee and right ankle were moderately tender to pressure and manipulation. The temperature was 99.4 F., the pulse rate 66, and the blood pressure was 90 mm. of mercury systolic and 60 diastolic. Systolic murmurs were heard at the aortic and mitral areas, but they became faint when the patient sat up.

*Use of Corticotropin.*—Intragluteal administration of corticotropin was begun June 10, and was continued as is represented in Figure 6. After thirty-eight days, injections were discontinued because the patient complained of headache and the blood pressure had increased to 200 mm. of mercury systolic and 92 diastolic. The current preparation of the corticotropin was found to be unsatisfactory; melanophore hormone was also found to be present. A total of 825 mg. of corticotropin was given.

After injections of corticotropin had been begun, articular pain was quickly abolished, the temperature returned to normal, bradycardia occurred, the P-R interval decreased, and the

sedimentation rate fell (Fig. 6). The albumin-globulin ratio rose from 1.1:1 to 1.4:1 in 29 days. The values for hemoglobin were not significantly changed.

Promptly after the injections of corticotropin had been discontinued the acute manifestations of rheumatic fever reappeared. Acetylsalicylic acid, which was now administered, promptly suppressed these acute manifestations. When the use of acetylsalicylic acid was discontinued, a second flare of the acute phase of rheumatic fever occurred, although in a milder form (Fig. 6). Without further treatment these manifestations of the acute rheumatic state subsided spontaneously in approximately two weeks.

*Murmurs.*—A systolic murmur of varying intensity was heard at the apex, to the left of the sternum, and in the aortic area throughout the patient's stay in the hospital. Some examiners heard a diastolic murmur to the left of the sternum, but it was not heard consistently.

The patient was dismissed from the hospital Aug. 28, 1949, in good general condition.

*Follow-Up.*—The patient was examined last April 5, 1950. Her last menstruation before her admission to the hospital had been on May 5, 1949, and she had resumed menstruation on Dec. 11, 1949. In January, 1950, stiffness, but no pain, of the left wrist, had developed in

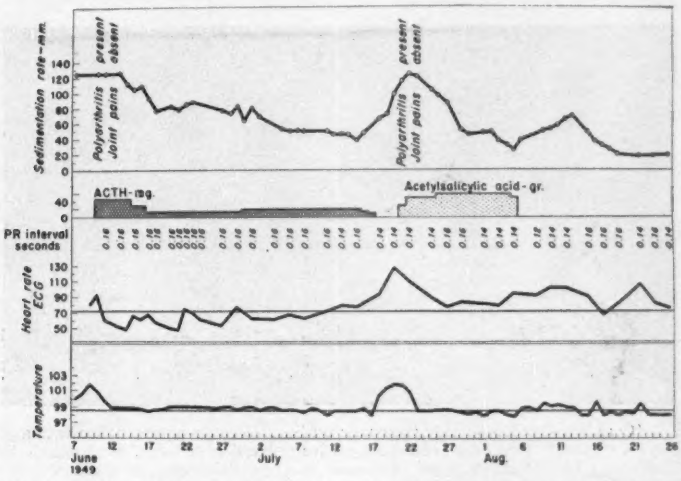


Fig. 6 (Case 8).—Effect of corticotropin on temperature, pulse rate, sedimentation rate, and P-R interval.

association with an acute infection of the respiratory tract, but these symptoms had disappeared without any known complications after she had been kept in bed for five days. At this examination (April 5) a murmur heard over the aortic area was transmitted to the vessels of the neck. The patient had attended school since September, 1949, and, except for avoiding running, she had engaged in about the same activity as other children, without evident cardiac embarrassment. The heart was not enlarged, the P-R interval was 0.14 sec., and the sedimentation rate was 15 mm.

### ACUTE RHEUMATIC FEVER IN THE FIRST ATTACK, WITHOUT PREVIOUS VALVULAR DAMAGE BUT COMPLICATED BY RHEUMATIC CARDITIS

CASE 9.—*History.*—A girl, 16 yr. of age, was admitted to the hospital Jan. 8, 1950. With the exception of a previous history of influenza, she always had been well. She gave no history of the usual diseases of childhood, and there was no history of previous rheumatic fever.

Beginning in the first week in December, 1949, and continuing for approximately four weeks, the patient had had migratory polyarthritis. Dyspnea, orthopnea, and a dry cough had occurred

on Jan. 1, 1950. During the first week of January the temperature had been elevated daily and had reached 104 F. On admission, the patient's chief complaints had been of dyspnea and of some residual pain and tenderness in her left hand and left arm.

*Examination.*—The patient weighed 174¾ lb. (79.2 kg.). She was dyspneic and cyanotic. Shallow respirations, with the rate varying from 32 to 48 per minute, occurred during the first few days of observation. The pulse was regular, and its rate was 120 per minute. A soft diastolic murmur was heard in the second and third interspaces at the left of the sternum. A pericardial friction rub was present. There were dulness to percussion and bronchial breathing over posterior and lateral aspects of the left side of the thorax. The breath sounds over the entire right side of the thorax posteriorly were moderately diminished.

A roentgenogram made at the bedside on the day after admission gave evidence of marked enlargement of the heart, passive congestion of the lungs, and probable bilateral pleural effusion (Fig. 7). The leukocyte count, which was 7,000 per cubic millimeter of blood on admission, rose to 20,500 on Jan. 16. It fell to 7,800 on Jan. 23 and to 5,000 on Feb. 6. On admission, the urine was of a specific gravity of 1.031; it contained albumin, graded 2, and this persisted throughout the patient's stay in the hospital. From time to time, pus and blood cells were found

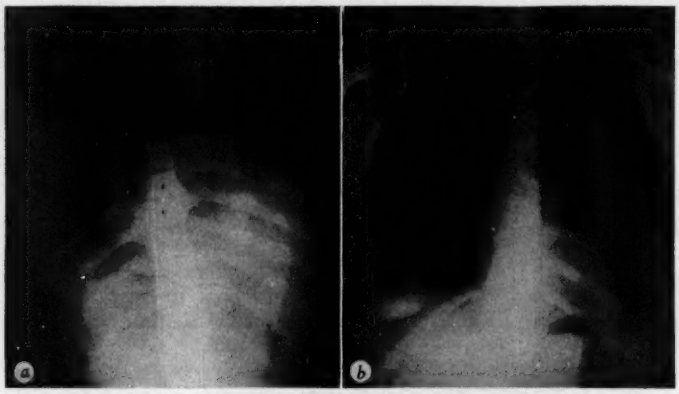


Fig. 7 (Case 9).—Diagnosis acute rheumatic carditis. Roentgenograms taken with a portable apparatus: (*a*) Jan. 9, 1950, heart enlarged, passive congestion of lungs, and probable bilateral pleural effusion; (*b*) March 9, heart of normal size. Administration of cortisone was begun Jan. 10 and discontinued Jan. 31, 1950.

on microscopic examination of the urine. When the latter findings were at a maximum, Escherichia coli grew on culture of the catheterized urine.

*Use of Cortisone.*—Intragluteal administration of cortisone was begun on Jan. 10, 1950, when 300 mg. of the hormone was given. The patient received 3.1 gm. of cortisone in 22 days (Jan. 10 to 31).

After cortisone first had been administered, pain in the shoulders disappeared, the temperature fell, the heart rate decreased, the P-R interval decreased, the sedimentation rate declined (Fig. 8), the value for hemoglobin rose from 10.3 to 12.6 gm. per 100 cc. of blood in 13 days, and the pericardial friction rub disappeared in seven days.

*Observation of the Heart.*—A pericardial friction rub was heard from Jan. 9 to 17, inclusive, but not thereafter. A short, harsh, systolic murmur at the apex was heard early in the girl's stay in the hospital, and it was present at the time of her dismissal. A diastolic gallop was first heard at the apex March 1, but it had disappeared by April 8.

Marked cardiac enlargement was observed in roentgenograms made at the bedside on the day after admission and on Jan. 17, 1950. In roentgenograms similarly made on Jan. 26, Feb. 1, and March 9, 1950, the size of the heart appeared to have decreased to the upper limits of normal (Fig. 7).

*Observations After Use of Cortisone Ceased.*—Shortly after administration of cortisone was discontinued, several manifestations of the acute phase of rheumatic fever reappeared (Fig. 8). At this time gallop rhythm was present. Despite this, administration of cortisone was not resumed. Approximately nine weeks was required for the rheumatic state to come to an end and for the mentioned abnormal manifestations to disappear (Fig. 8). We believe that cortisone should have been used much longer, either in a dose of 100 mg. daily or on alternate days, if we hoped to maintain suppression of the acute manifestations of rheumatic fever and thus minimize the chance of permanent cardiac injury.

The patient was dismissed in good general condition on April 22, 1950.

*Follow-Up.*—The patient was last re-examined one month after dismissal. She felt well and had been up eight hours daily. The systolic apical murmur, similar to that heard while the patient was in the hospital, was still evident. A teleroentgenogram revealed that the heart was normal in size and contour. The P-R interval was 0.14 sec., and the sedimentation rate was 15 mm. The urine contained no albumin and only an occasional pus cell.

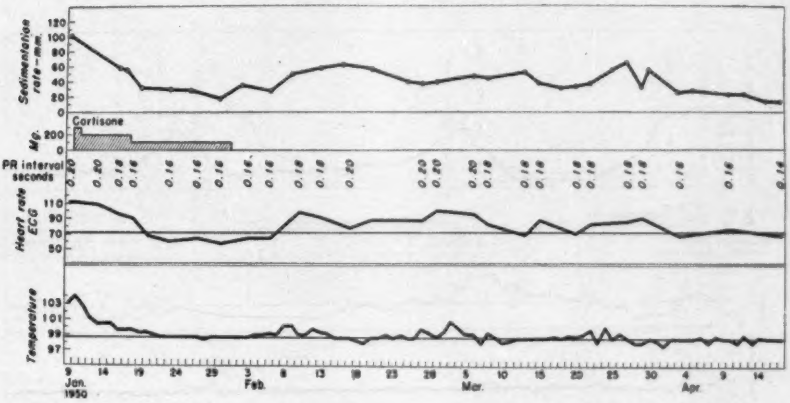


Fig. 8 (Case 9).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

CASE 10.—*History.*—A high school youth, 17 yr. of age, was admitted to the hospital on April 12, 1949. His past medical history was entirely insignificant; the family history contained no evidence of rheumatic fever or arthritis.

A sore throat and a mild cough on March 30, 1949, initiated the patient's illness. On April 1, and continuing until the patient's admission, migratory polyarthritis occurred, associated with fever, the temperature reaching a maximum of 103 F. on April 11. The youth was brought to the hospital because of dyspnea and substernal pain.

*Examination.*—The patient was acutely ill. He was unable to move in bed because of severe pain in his swollen ankles and toes. The temperature was 102 F., and the pulse rate 100 per minute. The blood pressure was 110 mm. of mercury systolic and 65 diastolic. Cardiac murmurs were not heard, and cardiac enlargement was not found at the initial examination.

*Use of Cortisone.*—Cortisone first was administered April 14 in a dose of 200 mg. Further details of its administration are given in Figure 9. A total of 4.3 gm. of cortisone was injected in 24 days.

After administration of cortisone was first begun, joint symptoms disappeared in five days except for tenderness over the right shoulder, which persisted one or two days longer; the temperature and heart rate returned to normal; the P-R interval decreased, and the sedimentation rate fell (Fig. 9).

Twelve days after administration of cortisone had been discontinued, on May 19, all the previous acute manifestations of rheumatic fever had reappeared. Cortisone was again administered, and a total of 3.1 gm. was given in 28 days. This was followed by prompt suppression of the rheumatic symptoms (Fig. 9).

After administration of cortisone had been discontinued a second time, acute manifestations of rheumatic fever occurred, consisting of increase in the sedimentation rate and P-R interval, and of fever, but without a flare of the polyarthritis. Without further medication these indices returned to normal in a little more than two weeks (Fig. 9).

*Observations of the Heart.*—A faint systolic murmur in the pulmonic area was first heard April 16 and intermittently thereafter. A soft aortic murmur first was heard April 25, and this persisted until the patient's dismissal. An electrocardiogram taken on April 13 contained changes which were considered to be indicative of pericarditis. While no pericardial friction rub ever was heard, a pleural friction rub was heard at the base of the right lung on April 14. The electrocardiogram had returned to normal on May 5 except for minor changes. On April 16, the heart appeared to be enlarged, since the apex beat could be palpated in the left anterior

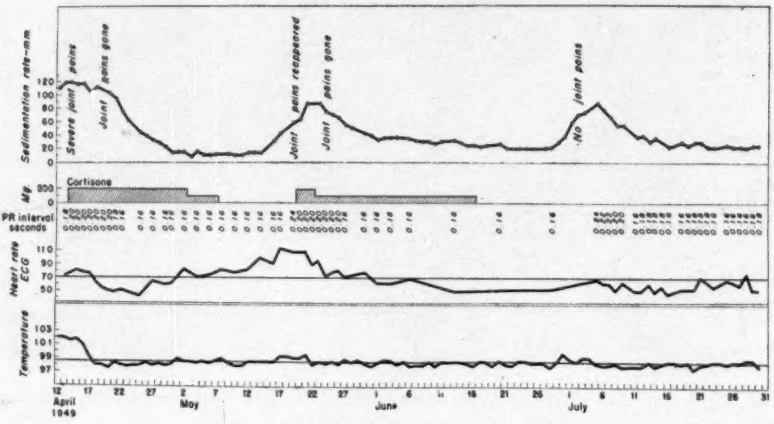


Fig. 9 (Case 10).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

axillary line. By April 22, the apex beat was observed to be just outside the nipple line. This clinical estimation of changes in the size of the heart could not be confirmed by comparison of roentgenograms taken at the bedside.

The patient was dismissed from the hospital in good general condition on July 31, 1949.

*Follow-Up.*—The patient was last examined April 6, 1950, eight months after dismissal from the hospital. He was in excellent health, had gone to school, and, in addition, had done manual labor. A soft systolic murmur was present at the aortic area. Only further observation will determine whether this murmur indicates the development of aortic stenosis. The teleroentgenogram revealed no enlargement or abnormality of the contour of the heart. The P-R interval was 0.14 sec. and the sedimentation rate was 21 mm.

*Comment.*—This case illustrates well the flare of rheumatic symptoms when administration of cortisone is discontinued before the rheumatic state has run its inherent course. To secure the most favorable outcome, we believe that administration of cortisone should have been carried out in such a manner as to prevent these flares.

ACUTE RHEUMATIC FEVER IN A RECURRENT ATTACK, WITH OR WITHOUT EVIDENCE OF DAMAGE TO THE HEART VALVES AND WITH OR WITHOUT PROBABLE PREVIOUS CARDITIS

CASE 11.—*History.*—A boy, 14 yr. of age, was admitted to the hospital on June 6, 1949, in his second attack of acute rheumatic fever. His previous diseases included measles, mumps, and scarlatina.

In 1945, he had had symptoms of acute rheumatic fever, consisting of migratory polyarthritis, for which he had been kept in bed for one month. The tonsils and adenoids had been removed shortly after this episode of illness had subsided.

The present illness dated from the onset of earache on April 13, 1949. On April 20, and for several days thereafter, the patient had had migratory polyarthritis. He had been kept in bed

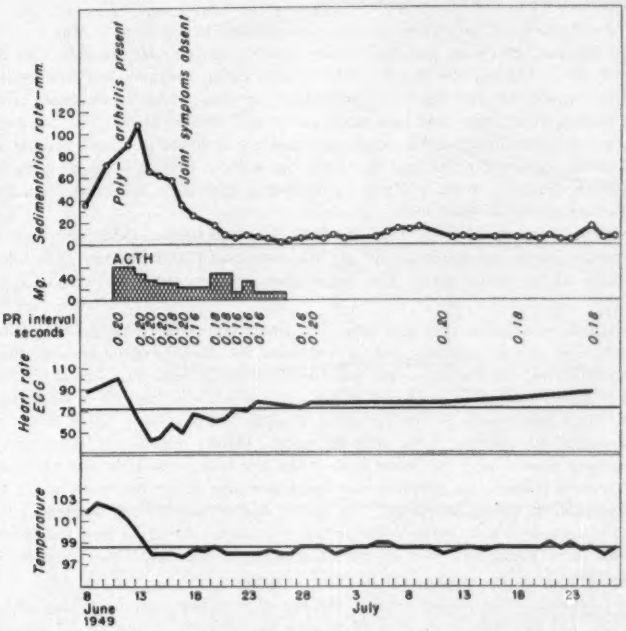


Fig. 10 (Case 11).—Effect of corticotropin on temperature, pulse rate, sedimentation rate, and P-R interval.

with this episode for 18 days and then had been allowed to increase his activities gradually until, at the end of two weeks, he had been up all day. Pain in the left ankle and pain and swelling in the right ankle had been observed June 2 to 5.

*Examination.*—On June 8, both ankles were acutely tender, swollen, red and hot, and the right wrist was acutely painful. The temperature was 101.8 F. on that day and 102.8 F. on the following day. A short systolic murmur was heard at the apex and was more pronounced when the patient was lying down than when he was sitting up.

*Use of Corticotropin.*—Administration of corticotropin was started June 11, 1949. The dosage is given in Figure 10, representing a total of 500 mg. in 16 days.

After administration of corticotropin had begun, the articular pain disappeared in six days; also the temperature dropped, the heart rate declined, the P-R interval decreased, and the sedimentation rate dropped after a brief rise (Fig. 10). There was no significant change in the

value for hemoglobin. The ratio of albumin to globulin was modified very little, probably because the ratio was normal from the beginning.

No flare of the acute manifestations of rheumatic fever followed cessation of use of corticotropin in this case (Fig. 10). An explanation for that may be furnished if one observes that injections of the hormone were not begun until approximately two months after the probable onset of the symptoms of rheumatic fever (April 20). By the time the course of corticotropin was finished, the rheumatic state probably had reached approximately the end of its natural duration.

The patient was dismissed from the hospital July 27, 1949, in good general condition.

*Follow-Up.*—The patient last was examined 10 months after his dismissal from the hospital. No cardiac murmur could be heard at rest, and only a very faint apical systolic murmur could be heard after exercise. It was not transmitted to the axilla and was not considered to be significant clinically. The heart was not enlarged. The boy had engaged in normal activities without any evidence of cardiac embarrassment.

CASE 12.—*History.*—A girl, 14 yr. of age, was admitted to the hospital May 9, 1949. At the age of 4 yr. she had had chorea and had become unable to walk or feed herself. This illness had lasted about three months. In March, 1942, a high fever, polyarthritis, and weakness had developed, for which the girl had been hospitalized for two weeks. A diagnosis of rheumatic fever and leakage of the heart had been made at the time of that illness. She had been kept in bed at home for an additional three months and had not returned to school until March, 1943. In March, 1945, fever and pallor had developed but without definite articular symptoms. Her home physician could not detect evidence of additional damage to the heart from this illness. She had had diphtheria in April, 1949.

Her present illness dated from April 26, 1949. She had become chilly and feverish. From that time to the time of her admission the girl had complained intermittently of pain in the neck and especially of substernal pain. The temperature had ranged from 101 to 102 F. each afternoon.

*Examination.*—The girl's skin was pale. The temperature was 101.8 F. The systolic blood pressure was 150 mm. of mercury, but to determine the diastolic pressure was difficult. The heart was overactive, and the pulse rate was 104 beats per minute. The second pulmonic sound was loud. A diastolic murmur was heard at the aortic area and to the left of the sternum in the second and third interspaces. A systolic and a diastolic murmur were heard at the apex. The point of maximal impulse was in the fifth interspace, slightly outside the left anterior axillary line. There was dulness over the lower lobe of the left lung posteriorly and rales were heard over that area; a friction rub, however, was not heard over either the lungs or the heart. The liver was palpable at the costal margin. The spleen was not palpable. A diagnosis of old aortic and mitral endocarditis with aortic regurgitation was made. Acute carditis was believed to be present because of a palpable liver margin, dyspnea, and cyanosis. The two latter conditions necessitated the use of an oxygen tent for their control.

*Use of Cortisone.*—The patient received 200 mg. of cortisone daily from May 12 to May 23, inclusive, and 100 mg. daily from May 24 to June 19, inclusive, a total of 5.1 gm. in 39 days.

Six days after administration of cortisone had begun, the temperature returned to normal. In two more days the girl was able to be out of the oxygen tent without dyspnea or cyanosis. The sedimentation rate dropped from 140 to 18 mm. in 17 days. The P-R interval decreased from 0.26 to 0.22 sec. in 18 days but never dropped below 0.20 sec. while the patient was under observation. The apical heart rate never was altered significantly by administration of cortisone. The hemoglobin per 100 cc. of blood rose from an initial value of 8.4 to 12.4 gm. in 16 days. The albumin-globulin ratio rose from 1.1:1 to 1.6:1 in 19 days and to 2.2:1 in 11 more days, partly owing to a rise in the albumin fraction and partly to a decrease in the globulin component. Particularly striking was the improvement in the patient's color, in her ability to eat, and in her general sense of well-being within five to seven days after cortisone first had been administered. There was no flare of acute manifestations of rheumatic fever after administration of cortisone had been discontinued.

*Observations of the Heart.*—During or after the administration of cortisone, there was no change in the heart murmurs or in the size of the heart as compared with the sounds and size observed at the initial examination.

The patient was dismissed July 14, 1949, in good condition. She had been up seven hours daily without untoward effects.

*Follow-Up.*—The patient was last examined nine months after her dismissal. She had not menstruated while in the hospital, but regular menstruation was resumed in October, 1949. There was no change in the cardiac murmurs as compared with those observed while the patient was in the hospital, and the teleroentgenogram indicated that the size of the heart had not diminished. The P-R interval was 0.24 sec. The patient had gone to school since September, 1949, walking a quarter of a mile to and from school without dyspnea.

CASE 13.—*History.*—A girl, 13 yr. of age, was admitted to the hospital Jan. 10, 1950. Previous diseases included measles and whooping cough. There was no family history of rheumatic fever.

Because of polyarthritis in April, 1949, a presumptive diagnosis of rheumatic fever had been made, for which the patient had been kept at rest in bed for eight weeks. In July, 1949, chorea had developed; it had responded to treatment with sedatives and salicylates, however, and the girl had been allowed to enter school in September.

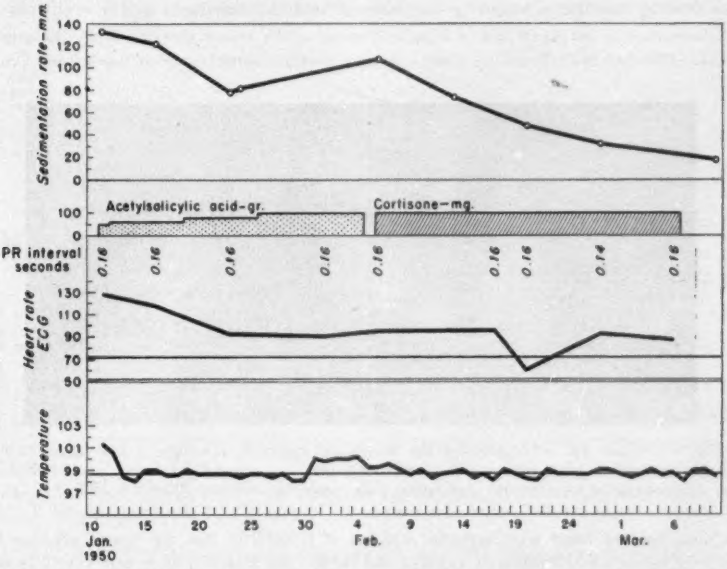


Fig. 11 (Case 13).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

The patient's present illness had begun Dec. 25, 1949, with chills, fever, and pain in a joint of the right big toe. She had been kept in bed at home until Jan. 2, when her physician had taken her to a hospital, where she had received salicylates, penicillin, streptomycin, and oxygen until her admission to the hospital in Rochester.

*Examination.*—On admission, the girl was cheerful and alert and cyanosis was not evident. Her respirations were 34 per minute, the pulse rate was 140 per minute, the beat was regular, and the temperature was 103 F. A systolic murmur, graded 2, was heard at the apex and was transmitted over the entire precordium and to the left axillary region. The point of maximal impulse was outside the nipple line. A pleuropericardial friction rub was heard over the fourth interspace to the left of the sternum. The bases of both lungs were dull to percussion, and breath sounds were decreased over those areas. Tubular breathing was heard over the lateral field of the left lung in the midaxillary line. A few fine rales were heard over the right lung posteriorly, at the angle of the scapula.

Jan. 11, 1950, a consultant observed that the heart was enlarged and overactive, that there was a notable rumbling systolic murmur at the apex, and that the pleuropericardial friction rub was still present. On that date a roentgenogram made at the bedside revealed cardiac enlargement, edema of the left lung, and diffuse opacity of the right hemithorax, attributable to pulmonary edema and pleural effusion. A diagnosis of recurrent acute rheumatic fever, carditis, and cardiac dilatation and failure was made.

From Jan. 10 to Feb. 5, inclusive, treatment consisted of rest in bed and administration of salicylates and digitalis. The amount of salicylate in the blood was found to be 23.0 mg. per 100 cc. The effect of this treatment on the sedimentation rate, P-R interval, temperature, and heart rate is shown in Figure 11.

*Use of Cortisone.*—Administration of cortisone was begun Feb. 6, 1950, and the patient was given 100 mg. daily from that date to March 6, inclusive. A total of 2.9 gm. was given in 29 days.

In general, the effect of cortisone on the sedimentation rate, heart rate, and temperature was more striking than that produced by acetylsalicylic acid and digitalis (Fig. 11).

*Observation of the Heart and of Venous Pressure.*—The venous pressure in the left arm on Jan. 13, 1950 had been 20 cm. of water. Since a roentgenogram made at the bedside Feb. 6,

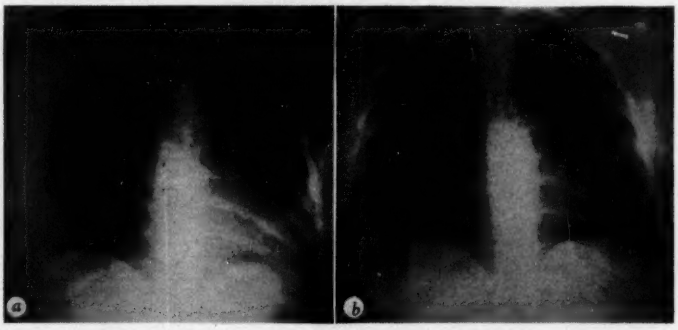

Fig. 12 (Case 13).—Diagnosis acute rheumatic carditis. Roentgenograms taken with a portable apparatus: (*a*) Feb. 6, 1950, heart enlarged; (*b*) March 13, heart much reduced in size. Administration of cortisone was begun Feb. 6 and discontinued March 6, 1950.

disclosed that the heart was markedly enlarged, it is unlikely that the venous pressure had decreased before administration of cortisone had begun. On March 9, three days after injections of cortisone were discontinued, the venous pressure was 9 cm. of water.

As noted previously, the heart was seen to be markedly enlarged in the roentgenogram taken at the bedside Feb. 6, 1950. While a roentgenogram made in a similar manner Feb. 20, gave evidence of moderate reduction in the size of the heart, it was still much enlarged. Roentgenograms taken at the bedside March 6 and 13, indicated that the heart was markedly reduced in size (Fig. 12). The girl's clinical improvement paralleled the decrease in the size of the heart.

The patient was dismissed March 19, 1950, with advice to continue rest in bed under the care of her home physician. Residence remote from Rochester has precluded the opportunity for subsequent examination.

*Comment.*—Probable marked reduction of the venous pressure and marked reduction in the size of the heart while the patient received cortisone are regarded as a favorable response in a case of rheumatic carditis. An even better result conceivably might have been obtained if administration of cortisone had been begun when the patient first entered the hospital.

CASE 14.[3]—*History.*—A girl, 12 yr. of age, was admitted to the hospital for the third time on Dec. 31, 1949. She first had been admitted on May 24, 1949, with acute rheumatic fever, after having been ill for about four weeks. At this first visit she had remained in the hospital 24 days. Her treatment had consisted of administration of acetylsalicylic acid, but her sedimentation rate at dismissal had been 83 mm. A soft, systolic, apical murmur was present. At the time of dismissal she had been advised to continue to rest in bed at home and to continue taking salicylates.

She had been admitted to the hospital a second time on June 21, 1949, because of precordial pain, fever, a rapid pulse, and a sedimentation rate of 91 mm. On treatment with salicylates, combined with rest in bed, the temperature had returned to normal, the pulse had continued to fluctuate about an average of 100 per minute, and the sedimentation rate had reached its lowest level (36 mm.) on Sept. 7, 1949. A blowing, systolic murmur had been heard at the apex. The diagnosis had been rheumatic carditis and mitral valvulitis. She had been dismissed from the hospital with instructions to take salicylates and to remain in bed at a nursing home.

The reason for her third and latest admission to the hospital, on Dec. 31, 1949, with which this study is most concerned, was the occurrence of anorexia and vomiting in the three previous weeks.

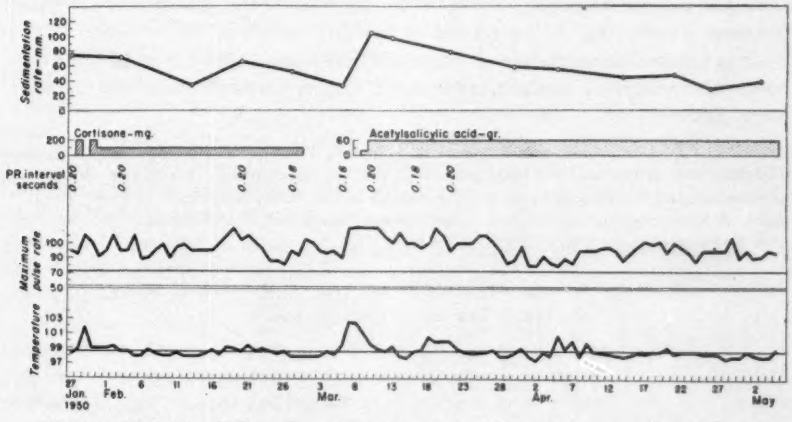


Fig. 13 (Case 14).—Effect of cortisone on temperature, pulse rate, sedimentation rate, and P-R interval.

*Examination.*—The girl was poorly nourished and pale. The blood pressure was 90 mm. of mercury systolic and 60 diastolic. The heart was greatly enlarged, its rate was 100 beats per minute, and a rough, systolic murmur was heard, loudest to the left of the sternum and in the left anterior axillary line.

*Use of Cortisone.*—From Dec. 31, 1949, to Jan. 27, 1950, the patient was kept at rest in bed and received supportive treatment, including use of digitoxin and phenobarbital but no salicylates. On Jan. 28, administration of cortisone was begun and was continued as is shown in Figure 13. A total of 3.3 gm. of cortisone was given in a period of 31 days.

The effect of cortisone on certain acute manifestations of rheumatic fever was not as striking as has been observed in other cases. However, it was somewhat greater than that produced by

3. This patient was regarded as having a recurrence of rheumatic fever at her admission Dec. 31, 1949. This interpretation is open to question because we do not know how completely she recovered after Sept. 7, 1949. It may be argued reasonably that she never recovered from acute rheumatic fever after her first admission to the hospital on May 27, 1949, and that thereafter the rheumatic process smoldered and fluctuated in severity until her last admission to the hospital.

the subsequent administration of salicylates (Fig. 13). Other effects associated with administration of cortisone were marked improvement in appetite and the conversion of an apathetic and uncooperative patient to one who was cooperative and more cheerful than before. The blowing, systolic, apical murmur persisted to the end of the period when cortisone was given. A roentgenogram made with a portable apparatus on Jan. 8, 1950, revealed marked cardiac enlargement. In the film made in a similar manner on March 6, marked reduction in size of the heart was evident, although the organ still was larger than normal. Whether similar reduction in the size of the heart would have occurred without the use of cortisone cannot be determined.

As revealed in Figure 13, the patient had a sharp increase in the active manifestations of rheumatic fever after administration of cortisone was stopped. She continued to receive acetylsalicylic acid until the time of her dismissal, May 6, 1950.

*Comment.*—Cortisone was administered to this patient to observe its effect in a case of rheumatic carditis of long standing. It could scarcely be anticipated that the hormone would reverse valvular injury, since the girl had been hospitalized twice previously for rheumatic fever. The improvement in the patient's general condition and the reduction in size of the heart while the patient was receiving cortisone possibly may be interpreted as beneficial effects of the hormone.

It is conceivable that better results might have been obtained from larger initial doses, plus continued administration of 100 mg. of cortisone daily over a much longer period.

*Follow-Up.*—The patient was last examined June 6, 1950, one month after her dismissal. The heart rate at rest was 110 beats per minute and the sedimentation rate 30 mm. A systolic murmur, graded 2, was heard and was transmitted to the axilla. A diastolic murmur was not heard. A teleroentgenogram indicated no appreciable decrease in size of the heart as compared with that evident in the film of March 6, 1950.

## SUMMARY OF MAJOR EFFECTS OF THE ADMINISTRATION OF CORTISONE AND CORTICOTROPIN

Administration of cortisone and corticotropin, in general, suppressed the acute manifestations of rheumatic fever. Usually, elevated temperatures returned to normal and joints became symptom-free in periods of five days or less. Excluding Cases 2 and 4 and three cases with carditis, Cases 12, 13 and 14, increased heart rates returned to normal, or below normal in the remaining cases, in an average of 5.3 days. Excluding Case 10, the heart rate in cases of rheumatic carditis returned to normal more slowly, if at all. Prolonged P-R intervals usually became normal in a period of three weeks or less. Sedimentation rates returned to a value of 25 mm. or less in an average of 18 days in 11 cases.

Blood pressure was not elevated in any case in which cortisone was given. One patient received an unsatisfactory preparation of corticotropin. In this case blood pressure increased to 200 mm. of mercury systolic and 92 diastolic, and it was necessary to discontinue use of the hormone.

Cardiac murmurs were characterized by their variability and intermittent character. Murmurs attributable to previous chronic rheumatic valvulitis were unchanged after use of the hormone. All diastolic murmurs, except in Case 12 (chronic aortic regurgitation), disappeared before the patients were dismissed from the hospital. Systolic murmurs persisted until the time of dismissal in all the remaining cases except Cases 1 and 5, in which all murmurs had disappeared before the patients were dismissed from the hospital.

The hearts of four patients (Cases 9, 12, 13, and 14) were markedly enlarged and rheumatic carditis was present at the time cortisone was first administered. Three of these patients had carditis unassociated with known previous cardiac damage. The hearts of two of these patients became markedly reduced in size during administration of cortisone. The heart of a third patient became only moderately decreased in size. A fourth patient had ancient, rheumatic, aortic and mitral endocarditis on which rheumatic carditis was superimposed. No reduction in the size of the heart resulted from administration of cortisone to this patient. It was concluded from the observations on these four patients that cortisone can exert a very beneficial effect on rheumatic carditis.

In six cases the concentration of hemoglobin was increased approximately 2 gm. per 100 cc. in an average period of two weeks while cortisone or corticotropin was administered. Similarly, the albumin-globulin ratio was increased in almost all cases in a period varying from two to five weeks. This increase was due chiefly to a decrease in the concentration of serum globulin and slight increase in the concentration of serum albumin.

The values for blood sugar, with the patient fasting, remained normal in our cases. The concentration of blood potassium remained normal or was reduced only slightly (below 4 mEq. in four cases). The blood potassium of one patient, who ate sparingly, was transitorily reduced to 2.8 mEq. The concentration of blood urea of one patient who received corticotropin rose to 77 mg. per 100 cc. It returned to normal after administration of corticotropin had been discontinued but increased moderately after the use of the drug was resumed.

Marked improvement in appetite and gain in weight often followed administration of cortisone and corticotropin. Similarly, an apathetic or apprehensive patient often became cheerful and optimistic.

A number of mildly objectionable effects attributable to the physiologic action of these hormones were observed. These included the temporary production of acne, of purplish striations of the skin, mild hirsutism and moon-shaped facial contour. Menses ceased under treatment but were resumed one to five months after use of cortisone or corticotropin had ceased.

### FLARES OF ACUTE RHEUMATIC FEVER AFTER WITHDRAWAL OF CORTISONE OR CORTICOTROPIN

Flares of acute rheumatic fever occurred in eight of 13 cases after cortisone or corticotropin had been withheld. Case 8 was excluded from this consideration because use of the hormone had to be stopped. Evidences suggesting exacerbation of the disease appeared as early as one day and as late as 17 days (average eight days) after discontinuance of use of the hormone. In one case each, cortisone and corticotropin were used and discontinued twice. Flares occurred after each omission.

Signs indicative of flares were fever, fast heart rate, lengthened P-R interval, and increased sedimentation rate. In general, an increased sedimentation rate was the earliest sign of a flare, although almost equally early was lengthening of the P-R interval. In several cases all the above indices appeared almost simultaneously. In some cases polyarthritis reappeared at a time when other indices of activity had reached their peak.

THE ACTIVE RHEUMATIC STATE AND THE LIMITED EFFECT OF TREATMENT

Any considerable experience with, and reflection on, patients with rheumatic fever leads one to the conclusion that patients who contract this disease have an inherent susceptibility. This is probably modified by age, environment, and the nature of the preceding infection. It is believed that the sensitizing agent enters by way of the respiratory tract. Given the sensitizing agent and inherent susceptibility of a host, there will result a widespread inflammatory reaction in mesenchymal tissues which will result in a mosaic of symptoms constituting the active rheumatic state. Such a situation, in the absence of treatment, can be expressed graphically (Fig. 14).

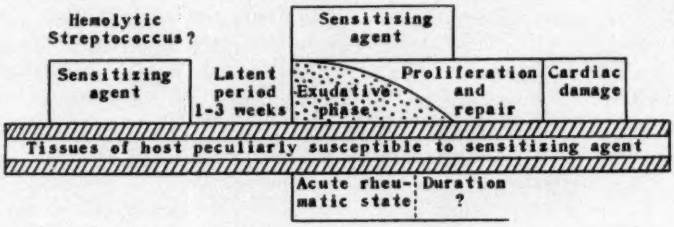


Fig. 14.—Schema indicating concepts of the reaction of the tissues of a susceptible host to the sensitizing agent of rheumatic fever; patient untreated.

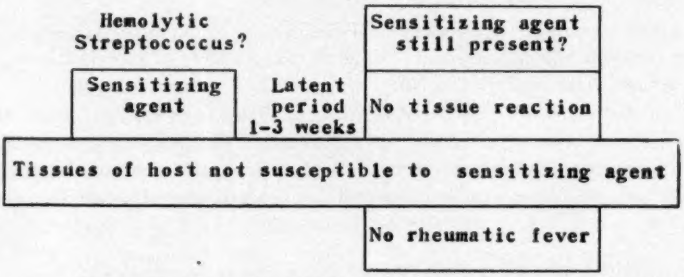


Fig. 15.—Schema indicating concepts of the reaction of patients whose tissues are not susceptible to the sensitizing agent of rheumatic fever.

The active rheumatic state, in the absence of treatment, comes to an end spontaneously, either by the patient's recovery or by his death. Thus, acute rheumatic fever is a self-limiting disease, and the duration of the rheumatic state may be regarded as being determined either by disappearance of the sensitizing agent or, less likely, but possibly, by continuation of the peculiar reactions of the tissues of the host beyond the time of disappearance of the sensitizing agent.

Many persons who are subjected to the same sensitizing agent as those who contract rheumatic fever have such resistance that the disease does not develop. This seems best explained by assuming that their tissues do not possess the peculiar tendency to react to the sensitizing agent that is possessed by the tissues of susceptible persons (Fig. 15).

We interpret our studies to indicate that cortisone or corticotropin does not cure acute rheumatic fever. They suppress the acute manifestations of the disease as long as adequate administration is continued, but a majority of our records indicate that one or many manifestations of the acute rheumatic state recur as soon as administration of the hormones is discontinued or inadequate doses are used.

When will such exacerbations cease? We believe that they will cease only when the exudative tissue reaction has run its course and we doubt that the course is shortened by use of cortisone or corticotropin. If, then, cortisone or corticotropin does not cure rheumatic fever or shorten its course, what value has either substance in treatment of this disease? In the reaction of the sensitized tissues of the host it is reasonable to assume that an exudative phase precedes a proliferative and reparative phase in the heart, and it seems likely that the former is a precursor of the latter. Further, in all probability, it is the latter phase that is responsible for permanent impairment of the heart. There is evidence that cortisone or corticotropin suppresses inflammatory reaction in mesenchymal tissues. It is further

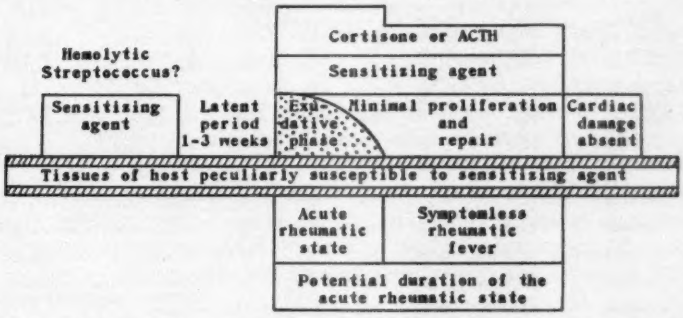


Fig. 16.—Schema indicating concepts concerning the modification of the reaction of the tissues of a susceptible host to the sensitizing agent of rheumatic fever; patient receiving cortisone or corticotropin.

assumed that since these hormones suppress the acute manifestations of rheumatic fever, suppression of the exudative inflammatory process in the heart is implied. If this assumption is correct, it is hoped that the proliferative and reparative stage of the disease will be forestalled (Fig. 16).

When we consider our cases in the light of these concepts, we have to conclude that our administration of cortisone or corticotropin was not planned to give the maximal protection to the patient with rheumatic fever.

Previously, attention has been called to the exacerbations of the manifestations of acute rheumatic fever which occurred in the majority of our cases after administration of the hormones had been discontinued. We are convinced now that these flares of the disease could, and should, have been prevented by longer use of cortisone or corticotropin. It is believed that a flare of the acute rheumatic state allows resumption of the exudative phase of the disease in the heart, thereby increasing the chance for development of the proliferative and reparative stage, which probably leads to chronic heart disease.

### GENERAL OBSERVATIONS ON THE ADMINISTRATION OF CORTISONE AND CORTICOTROPIN

*Time and Duration of Administration.*—It is advisable that these hormones be administered as early as possible after the onset of symptoms of acute rheumatic fever. Administration of the hormones should be continued until the active phase of rheumatic fever is at an end. How long will that be? Observation of our patients indicates that the active rheumatic state requires 6 to 12 wk., sometimes somewhat longer, to run its course. After these hormones have been administered four to six weeks, and if the acute manifestations of the disease have been brought under control, use of the hormones may be discontinued, provided that the patient is observed carefully for two weeks for the appearance of indices, previously described,

*Status of Heart Before and After Treatment with the Hormones*

| | | | Before Hormone Administered | | | Cardiac Signs at Intervals After Dismissal from Hospital | |
|---|---|---|---|---|---|---|---|
| Case | Hormone | Attack Treated | Duration of Disease, Days* | Valvular Damage | Carditis | Interval, Mo. | Signs |
| 1 | Cortisone | First | 4 20 | No | No | 9 | No murmurs; heart not enlarged |
| 2 | Cortisone | First | 12 20 | No | No | 10 | No murmurs; heart not enlarged |
| 3 | Cortisone | First | 7 22 | No | No | 1 | Faint systolic apical murmur; heart not enlarged |
| 4 | Corticotropin | First | 8 44 | No | No | 10 | No murmurs; heart not enlarged |
| 5 | Cortisone | First | 19 26 | No | No | 1.5 | No murmurs; heart not enlarged |
| 6 | Cortisone | First | 75 | No | No† | 2‡ | Systolic apical murmur†; heart not enlarged† |
| 7 | Corticotropin | First | 16 35 | No | No | 9 | No murmurs; heart not enlarged |
| 8 | Corticotropin | First | 14 26 | No | No | 7 | Systolic aortic murmur transmitted to vessels of neck; heart not enlarged |
| 9 | Cortisone | First | 40 | No | Yes | 1 | Apical systolic murmur grade 2; heart not enlarged |
| 10 | Cortisone | First | 13 15 | No | Yes | 8 | Faint systolic murmur at aortic area; heart not enlarged |
| 11 | Corticotropin | Recurrent | 52 59 | No | No | 10 | No murmurs; no cardiac enlargement |
| 12 | Cortisone | Recurrent | 16 | Yes | Yes | 9 | Well-compensated; murmurs and cardiac hypertrophy unchanged |
| 13 | Cortisone | Recurrent | 43 | No? | Yes | Not re-examined after dismissal | |
| 14 | Cortisone | Recurrent | 48 | Yes | Yes | 1 | Systolic apical murmur grade 2; heart still above normal size |

*Figures in left hand column were calculated from time of appearance of conventional symptoms of rheumatic fever; those in right hand column, from time of onset of precipitating infection.
† This observation was made before the recurrence of acute rheumatic fever.
‡ Had a recurrence of acute rheumatic fever after time of this examination.

which are to be regarded as evidences of persistence of the acute rheumatic state. If such indices reappear, they call for resumption of use of the hormones until such time as it seems advisable to revaluate the situation by cessation of their use and by careful observation of the patient for an additional two weeks.

*Amount of Hormone to Be Given.*—Definitive statements concerning the amounts of cortisone or corticotropin to be administered to patients with acute rheumatic fever cannot be made at this time. We believe that the usual practice of adjusting the amount of the hormone given to the age and size of the patient need be given little weight in treatment of acute rheumatic fever. It seems more important to gauge the amount of hormone used somewhat according to the severity of the disease. Initially, we believe that 200 to 300 mg. of cortisone or 60 to 100 mg. of corticotropin should be given daily until there is evidence that the acute manifestations of the disease are largely or completely controlled. After that, the

amounts should be decreased substantially, especially if the patients are children, to minimize side-effects. However, minor side-effects should not contraindicate adequate dosage should symptoms of acute rheumatic fever reappear. In some instances it possibly will suffice to give 100 mg. of cortisone every other day to maintain suppression of the acute rheumatic state.

A summary of some aspects of our cases is given in the Table.

### THE BASIC ACTIONS AND LIMITATIONS OF CORTISONE AND CORTICOTROPIN IN ACUTE RHEUMATIC FEVER

The opinion is often expressed that unless cortisone and corticotropin are effective weapons in the management of rheumatic carditis, their usefulness in rheumatic fever is open to serious doubt. Rheumatic carditis is encountered chiefly among patients who have recurrent attacks of rheumatic fever superimposed on hearts previously damaged by the disease. It is also encountered among patients with unusually severe rheumatic fever and, until now, no effective method of suppressing carditis of these patients has been known.

Cortisone and corticotropin have been likened to firemen whose function it is to put out a fire in its incipiency.[4] It is not to be expected that these hormones can assume the role of carpenters to restore a structure gutted by a previous conflagration. If cortisone and corticotropin are capable of blocking the exudative phase of rheumatic fever, then their administration in initial and recurring attacks of the disease may prevent or markedly minimize permanent cardiac damage (Fig. 16). If that could be accomplished, it is unlikely that carditis would be encountered often. Our results to date give us considerable reason to hope that early and adequate administration of cortisone or corticotropin in initial and recurring attacks of rheumatic fever and continuation of their administration until the disease has finished its active course will forestall permanent cardiac injury in the great majority of cases.

There was no reason to anticipate that patients whose rheumatic fever was suppressed by cortisone or corticotropin would be rendered immune to recurrence of the disease. Recurrences have been encountered in two of our cases (Cases 2 and 6).

It is not enough to extinguish the fire of acute rheumatic fever; fundamentally it remains as important as ever to prevent the initial and recurrent attacks if at all possible. Encouraging reports indicate that sulfonamides administered daily may prevent recurrences.[5] It also has been shown that penicillin administered intermittently may serve a similar, beneficial function.[6] Finally, early identification of respiratory infections with beta hemolytic streptococci and adequate treatment of

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4. Hench, P. S.: Introduction: Cortisone and ACTH in Clinical Medicine, Proc. Staff Meet., Mayo Clin. **25**:474-476 (Aug. 16) 1950.

5. Hench, P. S.; Bauer, W.; Boland, E. W.; Crain, D. C.; Freyberg, R. H.; Graham, W.; Holbrook, W. P.; Lockie, L. M.; McEwen, C.; Rosenberg, E. F., and Stecher, R. M.: Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Ninth Rheumatism Review), Ann. Int. Med. **28**:66-168 (Jan.); 309-451 (Feb.) 1948.

6. Kohn, K. H.; Milzer, A., and MacLean, H.: Oral Penicillin Prophylaxis of Recurrences of Rheumatic Fever; Interim Report on Method After a Three Year Study, J. A. M. A. **142**:20-25 (Jan. 7) 1950. Massell, B. F.; Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients with Rheumatic Fever, ibid. **138**:1030-1036 (Dec. 4) 1948.

these conditions with penicillin give promise of often forestalling the development of rheumatic fever.[7] However, until effective methods of prevention have been developed, it would be of the utmost importance to possess a means whereby the exudative phase of the disease could be suppressed, with the hope that proliferative and reparative processes in the heart, leading to permanent cardiac damage, could be averted. Cortisone and corticotropin give much promise of fulfilling this function.

## SUMMARY

Cortisone was administered to 10 patients and corticotropin (ACTH) to 4 patients who had acute rheumatic fever. The hormones seemed not to cure the disease or to shorten the usual duration of the acute rheumatic state. The acute manifestations of rheumatic fever were suppressed, but when administration of the hormones was discontinued exacerbations of the disease recurred until the disease had completed its usual course.

To be most effective, it appeared that cortisone or corticotropin should be given in adequate amounts early in the acute phase of the attack of rheumatic fever. Use of the drug in reduced amounts, given continuously or in courses, should be continued until it can be established that the activity of the disease is at an end.

Ten patients in their first attack of rheumatic fever and one (Case 11) in a recurrent attack of rheumatic fever may be considered in a group for purposes of evaluation of cardiac damage. Six of these patients, when re-examined at periods of one to 10 months after their dismissal from the hospital, had no cardiac murmurs or evidence of cardiac enlargement. Two of these patients subsequent to the period represented in the table have had recurrent attacks of rheumatic fever with reappearance of murmurs and cardiac enlargement.

Five patients who received cortisone had clinical evidence of carditis before the hormone was administered. It was concluded that the hormone exerted a definitely favorable effect on carditis in these cases.

Observation of these 14 patients over a much longer period will be required to determine whether permanent cardiac injury has been sustained and to evaluate the extent of the injury when present.

Other effects observed were marked improvement in appetite and morale, gain in weight, temporary production of moon-shaped facies, appearance or aggravation of acne, occurrence of reddish-purple striations over the thighs and buttocks, and amenorrhea among patients whose menses had become established. In only one case was it necessary to discontinue the use of these hormones, and in that instance it was owing to the use of an unsatisfactory preparation of corticotropin.

In one case, organic valvular defects and cardiac hypertrophy resulting from previous attacks of rheumatic fever were not modified by administration of cortisone. These hormones did not render patients immune to recurrence of acute rheumatic fever.

Our experience gives rise to considerable hope that the early, adequate administration of cortisone or corticotropin to patients in initial and subsequent recurrent

7. Denny, F. W.; Wannamaker, L. W.; Brink, W. R.; Rammelkamp, C. H., Jr., and Custer, E. A.: Prevention of Rheumatic Fever: Treatment of the Preceding Streptococcic Infection, J. A. M. A. **143**:151-153 (May 13) 1950.

attacks of rheumatic fever will prevent or markedly minimize permanent cardiac injury in the large majority of cases. Use of one or the other hormone for the treatment of acute rheumatic fever should be supplemented by the most effective prophylactic measures we can devise to prevent the occurrence or recurrence of this disease.

## ABSTRACT OF DISCUSSION

DR. STANLEY GIBSON, Chicago: Dr. Barnes was good enough to send me a copy of his paper, and I want to assure you that the brief review you heard this morning cannot represent the amount of work which has gone into this paper and the very accurate documentation of the cases which Dr. Barnes has presented.

There is one point that we as clinicians should take to heart in this discussion, that apparently the progress of rheumatic fever can be stopped or arrested in the exudative stage and that it does not go on to the proliferative stage, which we believe to be the important cause of the scarring of the myocardium and of the heart valves. If we can avoid this phase of rheumatic fever, something very important has been accomplished.

Dr. Barnes has approached chiefly the more or less acute case and, in most instances, in the first attack. My friend and fellow townsman, Dr. Dorfman, who is going to follow me in this discussion, has approached the problem from a somewhat different standpoint. He has purposely picked out cases of chronic active rheumatic carditis in which the patients are in more or less serious condition. I shall let him speak for himself, but I wanted to emphasize one point, that the effect of these hormones apparently is in some instances lifesaving. Otherwise, a patient would continue to go downhill and succumb. I think that is very important.

At the meeting of the American Pediatrics Society in French Lick, Ind., last month, Dr. May Wilson and her group from New York gave a report which to me was extremely interesting. I wrote to Dr. Wilson and asked her if she would give me a summary, so that I might quote her accurately.

She studied the effects of the hormones on 10 children very early, in the acute stage of rheumatic carditis. There was a normal temperature in 12 to 24 hours; cessation of myocarditis by the third day as evidenced by general well-being; disappearance of precordial distress; drop in respiration and pulse rate; improved quality of heart sounds; and disappearance of new murmurs, and of electrocardiographic abnormalities. There was increase in vital capacity to the normal within a few days. That she particularly stressed because she said she had never seen that in any instance of acute rheumatic carditis when these hormones were not given. She concluded that the acute rheumatic process was abolished or at least interrupted. In her follow-up, she found no signs of activity.

Now, the interesting point is that she gave corticotropin in doses of 50 to 100 mg. daily for about four days, and a smaller dose through the last three days; use of the drug was discontinued at the end of one week. This report is particularly optimistic, perhaps because the cases were very early.

I believe that Dr. Barnes stated that in five of his 14 cases the rheumatic state was terminated. I wonder whether he remembers whether those cases were extremely early or whether the rheumatic process had been going on for only a very few days.

What is the present status of the rheumatic fever problem? I think it is extremely encouraging. Last week, Dr. Rammelkamp, of the American Heart Association, stated that if we could treat a patient susceptible to rheumatic fever in the first day or two of his preceding streptococcic infection, we could, by administering penicillin for two or three days in adequate dosage, prevent in the great majority of cases the rheumatic fever which is likely to follow in a period of two to three weeks.

I was particularly glad to hear Dr. Rammelkamp say that in about 90 per cent of the cases one could by inspection of the throat and palpation of the cervical nodes make a clinical diagnosis of hemolytic Streptococcus infection without having to resort to bacteriological studies.

Now, finally, in prevention, we have the use of sulfonamides and also of penicillin for the prevention of recurrent attacks in patients who are recovering from rheumatic fever. I do not believe those means are used as much as they should be. I think, in the present state of our

knowledge, that sulfonamides are probably superior to penicillin. They should be given, if at all, over a long period without interruption, and, naturally, the patient must be checked for possible side-effects.

Of course, years of observation are necessary before we know the ultimate effects of these hormones upon active carditis, but certainly the situation looks hopeful and it is tremendously exciting.

DR. ALBERT DORFMAN, Chicago: It is a real privilege to have heard Dr. Barnes's paper. As Dr. Gibson has said, this represents such a small part of the very beautiful job of investigation.

Our own studies have been done quite purposely somewhat differently, in that patients with long-standing active carditis have been selected. This was done originally in order to get an answer to some of the questions that Dr. Barnes has already mentioned; whether this treatment acted as a repressive measure or changed the course of the disease; also whether it actually repressed the carditis. I can say briefly that in those patients who have been ill for a long time there has been a uniform result in that the evidences of active carditis have been repressed, with diminution of heart disease, disappearance of friction rubs, and disappearance of congestive failure; with withdrawal of the drug, in general, there has been a reactivation of the disease, suggesting that primarily the treatment has only repressed the disease rather than changed its course.

I think there has been very little question that the effects of the drug have not been solely on fever, arthritis, and other more superficial manifestations but have actually been on the active carditis. It would seem, then, that I could add our experience as extremely hopeful in the possibility that in the usual type of acute rheumatic fever one might be able to repress the exudative phase of the carditis during that time and in that way decrease the amount of heart damage that might occur later.

I think that at the moment we still have to take this as a preliminary conclusion and only a long-term study will give us the final answer; we do not know whether subtler changes are occurring which may produce heart damage.

I should like, along with Dr. Gibson, merely to mention the fact, not to disagree with Dr. Barnes because our philosophy has been exactly the same as his, that Dr. Wilson's work and some of the work by Dr. Massell, which was reported last week before the American Rheumatism Association, has suggested that possibly the drugs may change the actual course of the disease. Personally, I do not feel we are at a point that we can argue about this. I think it is a matter of different experiences, and until we all have much more experience the answer will not become more obvious.

DR. PHILIP S. HENCH, Rochester, Minn.: I appreciate very much the invitation to come here. I did not expect to speak, and all I want to say is that Dr. Barnes, in studying these patients with us, in my opinion has done a beautiful job in trying to analyze the important problem as to whether this treatment really shortens carditis or influences carditis.

If cortisone has no influence on carditis, then it certainly has a limited place in the management of rheumatic fever, but I believe with Dr. Barnes that the drug does have a distinct place in the management and eventual prevention of rheumatic carditis and that it will suppress the manifestations which eventually produce the permanent cardiac lesions. I am particularly happy to know that cortisone is effective by mouth. My colleagues and I used a mixture of compounds E and F a year ago, which was effective when given orally and then Dr. Freyberg this week announced the effectiveness of pure cortisone given by mouth for rheumatoid arthritis. It most certainly will make the problem an easier one for the pediatricians.

I think that Dr. Barnes's main contribution is his excellent study of the underlying mechanism and the extent to which these substances have modified it. I agree with him that in these acute rheumatic states the duration is probably not shortened, but we have now two hormones with which we can suppress the manifestations of the acute rheumatic state.

DR. ARLIE R. BARNES, Rochester, Minn.: In regard to the question that was posed by Dr. Gibson concerning the nature of the cases in which observation indicated that we had actually,

as far as observed, completely abolished the disease—that is, there were no murmurs and no cardiac enlargement—four of them were cases in the first attack of rheumatic fever and the fifth one was that of a patient with recurrent acute rheumatic fever.

I may say that two of the patients were extremely ill at the time they came in. However, none of those patients had what I should call good criteria of carditis. By that I mean enlargement of the heart, pericarditis, or other signs like congestive failure. I think that we must agree with Dr. Dorfman that we must keep an open mind about the question of whether or not these hormones shorten the disease. I may say this, that eight of our 14 patients after the omission of cortisone or corticotropin, had quick reappearance of manifestations of the disease.

Now, in one or two in which this did not occur, it was interesting that our treatment had started at about the sixth week of the disease and extended over a period of four weeks; therefore the failure of the symptoms to reappear meant to me that we simply treated the patient in his terminal natural duration of the disease; this may account for some of the failures of reappearance of symptoms. But that question is relatively unimportant.

I should like to say one thing before closing: We think it is quite important that these hormones be administered as early as possible after the onset of acute rheumatic fever; that is to say, if one waits as long as a month after the onset, the chances of having a complete suppression of the disease and of abolishing the after-effects certainly seem less to us than in those patients who receive treatment in the first two weeks of their illness.

# SIMPLE PROCEDURE FOR CATHETERIZING GIRLS

HENRY F. HELMHOLZ, M.D.
ROCHESTER, MINN.

AS A RESULT of a recent discussion of catheterization of female patients for bacteriologic study of the urine, it became evident that a great variety of technics are being used at the present time. The information given in some textbooks on urology, on pediatrics, and on laboratory diagnosis is merely that for bacteriologic examination of the urine of the female a catheterized specimen must be obtained, and if a definite technic of catheterization is described it usually is rather complicated and necessitates washing the hands several times, washing the vulva, and the application of antiseptics.

For many years, I have been using a very simple technic for the catheterization of female infants and children, which is also applicable for adults. The following equipment is used for catheterizing girls: (1) a short glass catheter which is 3 in. (7.6 cm.) long and one-eighth inch (0.32 cm.) in diameter, to which is attached a rubber tube 2 in. (5 cm.) long; (2) a pressure wash bottle (Figure), to which is attached a rubber tube with a spring clamp and a small nozzle, and (3) a rubber bulb having a one-way valve to build up pressure and a screw clamp to hold it. The spring clamp controls the flow of the irrigating solution, a 1 : 1,000 solution of benzalkonium (zephiran®) chloride. The only modification that has been made in the original model has been to shorten the length of the catheter from 17 to 7.5 cm. in order to do away with the danger of the catheter being broken by a sudden arching of the child's back after the catheter has been passed into the bladder.

The catheter can be boiled immediately before it is used, or, for convenient use in the hospital, dispensary, or office, it can be put in a test tube (Figure) which also contains a wooden applicator wound at one end with a generous amount of absorbent cotton (purified cotton U. S. P.). The test tube is wrapped in a towel and sterilized in an autoclave. The test tube is used to hold the specimen obtained by catheterization. The applicator is used to dry the urethral meatus after it has been washed with the antiseptic solution. If a pressure wash bottle is not available, a number of cotton pledgets soaked in a 1 : 1,000 solution of benzalkonium chloride is used to cleanse the areas immediately about the meatus.

The following technic has proved useful and has not proved objectionable to the patient. The hands should be washed before catheterization of the patient is begun. The child is told that this procedure will not hurt her. In cases in which previous catheterization has been painful, several attempts at catheterization may have to be made before the child will cooperate.

The catheter and applicator are laid out on the towel in which the catheter has been sterilized, or they are left in the test tube so that they can be withdrawn without

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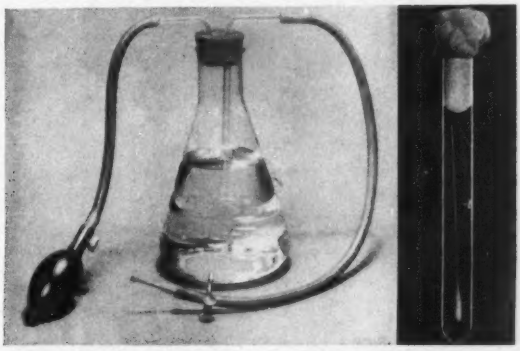
contamination. Pressure is then built up within the wash bottle, which is placed so close that the nozzle of the tubing from the wash bottle can be brought close to the vulva. Catheterization then can be performed without any assistance if the patient will cooperate. In cases in which infants and small children are uncooperative, the arms and head are held by mother or nurse, and, if a second helper is not available, the person doing the catheterization holds the patient's left leg outward with the back of his left hand and with the elbow of his right arm holds the right leg in abduction.

The labia are held apart with the thumb and index finger of the left hand. The spring clamp is picked up with the right hand, and a stream of 1 : 1,000 solution of benzalkonium chloride is applied to the area immediately surrounding the meatus. After thorough washing, the meatus is dried with the cotton applicator.

The sterile catheter is then grasped in the right hand in the area covered with rubber tubing and introduced slowly into the urethra. The catheter is held very loosely and is introduced with a minimum of force. After the catheter has been



Pressure wash bottle and sterile catheter and applicator in test tube.

introduced a short distance, it takes an upward turn and enters the bladder more nearly parallel with the long axis of the body. Just before it enters the bladder, slight resistance usually is encountered. At times this resistance may be considerable. With waiting a few moments, the spasm of the sphincter usually will relax and the catheter will pass into the bladder without further difficulty. As soon as a few cubic centimeters of urine are obtained, the rubber tubing is compressed and its end inserted into a sterile test tube. The specimen is obtained by releasing the pressure on the rubber tube.

The urine should be cultured within two or three hours. From 0.5 to 1 cc. of the urine should be used to inoculate a plate of eosin-methylene-blue agar. If the presence of streptococci is suspected, a culture also should be made on blood agar. The sediment should be stained by Gram's method in order to determine whether Gram-positive cocci or Gram-negative bacilli predominate.

In small children and infants the entrance of the catheter into the bladder may bring a gush of urine from around the catheter. The end of the rubber tube can usually be kept uncontaminated, and a clean specimen can be obtained.

In newborn infants and in premature infants it may be impossible to pass the usual glass catheter, and a small metal catheter, 0.2 cm. in diameter and 3 cm. in length, should be used. It is also important to know that in early infancy there is frequently a fold of mucous membrane lying over the urethral meatus. In order to insert the catheter into the urethra, it must be held in a position almost parallel to the long axis of the body, passed caudad for a short distance back of this fold, swung upward, and passed downward into the urethra. On further introduction, it must be swung through an arc of 90 degrees to enter the bladder. In passing the catheter downward, one not infrequently misses the urethra, and the catheter enters the vagina instead. If this occurs, a fresh catheter must be obtained, or the used one resterilized.

On occasion, the bladder may be practically empty, and one may obtain only enough urine to fill the catheter. If the rubber tubing is held compressed and the catheter withdrawn, a sufficiently large specimen of urine for culture can be obtained by allowing the urine to run out through the rubber tubing into a sterile test tube.

# PERIANAL DERMATITIS OF THE NEWBORN

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PERIANAL dermatitis of the newborn is a common eruption which is not described in leading American dermatologic and pediatric textbooks.[1] This may be because of confusion with the well-recognized napkin dermatitis. The two differ, however, in location, age incidence, and cause.

Napkin dermatitis is also called diaper eruption, erythema gluteale, and erythema of Jacquet. This, in the words of Cooke,[2] is a dermatitis "limited to the convex surfaces of the thighs and buttocks since the approximated flexures and the sulci between them are protected from constant contact with the diaper and ammonia." The perianal dermatitis, on the other hand, is an irritation of the skin about the anus. It is erythematous, red, and frequently exudative. Patients with severer disease show multiple small superficial ulcerations. The involved area varies from 3 to 4 cm. in diameter and centers at the anus. The inflammatory reaction fades gradually at the periphery. Many cases of mild disease will not be noticed unless the buttocks are manually separated.

Andrews [3] states that the napkin dermatitis occurs in infants over 3 months of age. Cooke's [4] view is in agreement when he reports that the napkin dermatitis is far more commonly found during the latter part of the first year of life. In contrast, the perianal dermatitis is common during the first week of life.

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This work was done at the Maternity Nurseries of the Cooper Hospital, Camden, N. J., with the cooperation of Dr. George B. German, Obstetrician and Dr. Vincent P. Del Duca, Pediatrician.

1. (*a*) Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood: A Textbook for the Use of Students and Practitioners, revised by L. E. Holt Jr. and R. McIntosh, ed. 11, New York, D. Appleton-Century Company, Inc., 1940. (*b*) Mitchell, A. G., and Nelson, W. E.: Mitchell-Nelson's Textbook of Pediatrics, edited by W. E. Nelson, ed. 4, Philadelphia, W. B. Saunders Company, 1946. (*c*) MacKee, G. M., and Cipollaro, A. C.: Skin Diseases in Children, ed. 2, New York, Paul B. Hoeber, Inc., 1946. (*d*) Andrews, G. C.: Diseases of the Skin for Practitioners and Students, ed. 3, Philadelphia, W. B. Saunders Company, 1946. (*e*) Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947. (*f*) Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939. (*g*) Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 7, Philadelphia, Lea & Febiger, 1948.

2. Cooke, J. V.: Dermatitis of the Diaper Region in Infants (Jacquet Dermatitis), Arch. Dermat. & Syph. **14**:539 (Nov.) 1926.

3. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 116.

4. Cooke, J. V.: The Etiology and Treatment of Ammonia Dermatitis of the Gluteal Region of Infants, Am. J. Dis. Child. **22**:481 (Nov.) 1921.

It is generally accepted that ammoniacal urine is the usual cause of napkin dermatitis. Cooke [4] has shown that this can be brought about by fecal bacteria which split the urea of the urine, forming ammonia, which damages the skin of the napkin area. In the present study the odor of ammonia was not detected in any of the cases of perianal dermatitis, and the evidence indicated that the cause is alkaline feces.

An examination of nearly 1,100 babies was made initially. There were 879 white babies, 590 of which were breast-fed and 289 bottle-fed. There were 217 Negro, or part Negro, infants, 190 breast-fed and 27 bottle-fed. Their ages when examined varied from 2 to 20 days, the great majority being between 3 and 7 days old. Of the 590 breast-fed white babies, 42 had some degree of irritation at the anal area. This amounted to 7.1%. This tendency to irritation increased with each of the first few days of life, as illustrated by the following tabulation of data on breast-fed white babies:

| Age, days | 2 and 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|
| No. not irritated | 102 | 131 | 128 | 107 | 58 | 18 | 3 | 1 |
| No. irritated | 2 | 6 | 15 | 14 | 4 | 1 | .. | .. |
| % irritated | 2 | 4.4 | 10.5 | 11.5 | 6.4 | .. | .. | .. |

The 289 white infants which were bottle-fed included 102 with perianal dermatitis, or 35.3%. The following tabulation of data on bottle-fed white infants (receiving cow's milk and dextri-maltose®) indicates that the tendency to irritation increases with the duration of bottle feeding up to and including five days:

| Duration, days | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| No. not irritated | 31 | 38 | 40 | 26 | 20 | 16 | 16 |
| No. irritated | 7 | 11 | 16 | 29 | 27 | 7 | 5 |
| % irritated | 18.4 | 22.4 | 28.5 | 52.7 | 57.4 | .. | .. |

It should be noted that the days referred to above are days of bottle feeding and not the age of the infant. Some infants were bottle-fed from birth, and others were breast-fed for various lengths of time before being started on a bottle.

The results in the case of the Negro infants were such that they were not combined with the tabulation regarding the white babies. One hundred and ninety of the Negro babies were breast-fed, and none had any degree of anal or perianal irritation. The 27 Negro babies which were bottle-fed included only three with a dermatitis. One was bottle-fed for only one day, one five days, and one seven days.

The stock formulas used varied with the age of the infants. Only water was given the first 24 hr. During the second and third days 3 oz. (90 ml.) of evaporated cow's milk, 15 oz. (450 ml.) of water, and 1 tablespoon (15 ml.) of dextri-maltose® No. 1 (containing 2% sodium chloride), divided among six bottles, was given daily. The formula for the fourth and fifth days was 4.5 oz. (135 ml.) of evaporated milk, 13.5 oz. (400 ml.) of water, and 1.5 tablespoons (23 ml.) of dextri-maltose® No. 1, divided into six portions. Beginning with the sixth day and continuing thereafter the babies received 5 oz. (150 ml.) of evaporated milk, 13 oz. (385 ml.) of water, and 2 tablespoons (30 ml.) of dextri-maltose® No. 1. A few of the babies received special formulas.

The routine care of the skin at the anal area, buttocks, and posterior thighs was removal of fecal matter at each diaper change with plain warm water on cotton sponges followed by application of light liquid petrolatum. If any degree of dermatitis was present at the perianal skin, a cod liver oil ointment was applied. In cases of severe disease the diaper was removed, the infant kept on its abdomen,

and a 100-watt incandescent bulb placed about 18 in. (46 cm.) above the buttocks. This procedure usually resulted in healing within a few days.

On the assumption that a change in carbohydrate from dextri-maltose® to lactose would result in a more acid stool approaching that of a breast-fed baby, the formulas were changed and an additional 253 white babies examined. The change in formulas consisted solely in substituting an equal volume of lactose for the dextri-maltose.®

The over-all result was that 60 of the 253 babies were found to have a perianal dermatitis. This amounted to 23.7%. In this new series the tendency to have perianal irritation also increased with the number of days of bottle feeding, as

Perianal dermatitis of the newborn. The peripheral darkening of lateral thighs and hips is shadow.

shown by the following tabulation of data from bottle-fed white infants receiving cow's milk and lactose:

| Duration, days | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| No. not irritated | 12 | 57 | 60 | 29 | 23 | 12 |
| No. irritated | 4 | 7 | 21 | 13 | 8 | 7 |
| % irritated | .. | 11 | 26 | 31 | 26 | 37 |

None of the 1,349 babies had the napkin dermatitis of the convex surfaces of the thighs and buttocks, and the ammoniacal odor of the urine associated with that condition was not present.

## COMMENT

Ammoniacal urine can hardly be the cause of perianal dermatitis because its characteristic odor was not detected in any of these cases. In addition, the eruption occurred in some of the breast-fed and some of the bottle-fed babies as young as 3 and 4 days, at which time they were still passing meconium stools. Grulee and Sanford [5] state that meconium is sterile and resistant to bacterial action.

5. Grulee, C. G., and Sanford, H. N.: The Newborn, in Brennemann's Practice of Pediatrics, edited by I. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 1, Chap. 42, p. 14.

It is likelier that perianal dermatitis is caused by alkalinity of the stools of susceptible babies. According to Holt and McIntosh [6] the stool of the breast-fed infant has a pH of 5.5 to 6.5, while the reaction of the stool of the bottle-fed baby is more alkaline, having a pH of even 7.0 or higher. In this study the infants with the most acid stool, the breast-fed babies, had the lowest incidence of perianal dermatitis. The group on cow's milk and dextri-maltose® had the greatest number with perianal irritation.

In two respects perianal dermatitis of the newborn and napkin dermatitis are alike. They are both less common in breast-fed than in bottle-fed babies, and Negro children are relatively insusceptible.[2]

The differences in percentages of perianal dermatitis occurring in the babies fed dextri-maltose® (35.3%) and in those fed lactose (23.7%) appears to be large. However, when the figures are viewed statistically, the difference is not so great. The standard error [7] is calculated by the formula $\sqrt{\frac{p \times q}{n} + \frac{p \times q}{n}}$, where $p$ is the percentage of babies with perianal dermatitis in each of the two groups and $q$ is the percentage without and $n$ represents the number in each of the two groups.

$$\sqrt{\frac{35.3 \times 64.7}{289} + \frac{23.7 \times 76.3}{253}} = 3.85$$

The observed difference in the two groups of bottle-fed babies was $35.3\% - 23.7\%$, or 11.6%, while a difference of twice the standard error, namely 7.7% ($2 \times 3.85$), might have arisen by chance.

## SUMMARY

Perianal dermatitis of the newborn is a common eruption not described in leading American textbooks of dermatology and pediatrics. It occurs in a different location than diaper eruption, at an earlier age, and is probably caused by alkaline feces rather than ammoniacal urine.

In a maternity nursery 1,349 babies were examined. Of the 590 breast-fed white infants, 7.1% had some degree of perianal irritation of the skin. None of the breast-fed Negro babies were so affected.

Of 289 white infants fed a formula of cow's milk, water, and dextri-maltose,® 35.3% had some degree of perianal dermatitis, while 23.7% of 253 white infants fed the same formula except with lactose in place of dextri-maltose® were so affected.

No instances of napkin dermatitis were found.

516 Cooper St.

6. Holt, and Howland,[1a] p. 170.

7. Hill, A. B.: Principles of Medical Statistics, ed. 5, London, The Lancet, Ltd., 1950, p. 111.

# PORTABLE HUMIDIFYING UNIT

## II. Large-Capacity Metal Nebulizer

ROBERT DENTON, M.D.
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AND
ROBERT M. SMITH, M.D.
BOSTON

IN A PRELIMINARY report [1] a device for supplying a supersaturated atmosphere and high oxygen concentrations has been described. This method of therapy is also known as continuous oxygen-aerosol or cold humidification therapy. The apparatus for this therapy was designed to fulfil the following requirements: (1) to produce a supersaturated atmosphere of nebulized particles (a visible mist) within a Collins Oxyflo Open Top (formerly Burgess-Collins) Oxygen Tent; (2) to maintain an oxygen concentration at 60 vol. % or more, and (3) to provide a means for controlling the temperature within the tent. The following additional attributes were felt desirable: (1) that such equipment should be easily portable and so available anywhere in the hospital or in the home; (2) that the equipment should be simple to operate and maintain, and (3) that the cost of such equipment should be reasonable.

The original apparatus consisted of a plastic Vaponefrin nebulizer adapted to fit into a constant-feed reservoir.[1] Experience with the clinical application of this device was encouraging, and it proved of great practical advantage in the care of infants and children with inflammation or obstruction of the respiratory tree. The main problems encountered with these original units were clogging of the small jets of the nebulizer, difficulty in achieving optimal volumes of nebulized mist, and breakage. Further efforts to improve this equipment were directed toward construction of a nebulizer with removable metal parts.

### EQUIPMENT

The metal mist generator (Fig. 1) is an automatically feeding metal nebulizer fitted over a glass-jar reservoir. It is constructed of aluminum alloy treated with the alumalite [2] process. The atomizer unit within the nebulizer housing is made of stainless steel. All surfaces are nonreactive and noncorrosive. The atomizer jet can be removed quickly should particles from the oxygen line obstruct the lumen. A replaceable filter prevents clogging of the feed tube.

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Dr. Denton is a resident at Children's Hospital of the East Bay and Dr. Smith director of the Department of Anesthesia, Children's Medical Center.

This work was supported by a grant from the $MistO_2$ Gen Equipment Division of the Production Foundry Co., Oakland, Calif. $MistO_2$ Gen is the commercial name of the metal nebulizer.

1. Smith, R. M., and Denton, R.: Portable Humidifying Unit, Am. J. Dis. Child. **81**:784 (June) 1951.

2. Aluminum Co. of America, Pittsburgh.

When the oxygen gauge is opened, the solution in the glass reservoir is drawn up through the feed tube and then atomized. These large atomized particles pass through a system of baffles, where they are broken into nebulized particles, ranging in size from 0.5 to 10 μ. With particles of this size the mist is distributed most advantageously throughout the tracheobronchial tree (Abramson [3]).

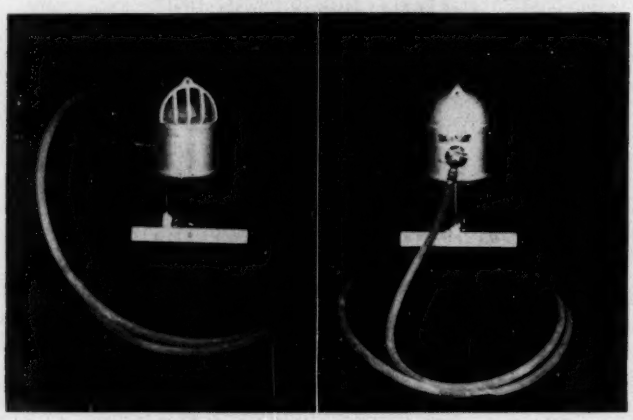

Fig. 1.—Front and side view of metal mist generator (Mist$O_2$ Gen nebulizer) with oxygen tube attached. Note the thumb screw at the point of attachment of the oxygen tube. When this is removed, the atomizer jet may be withdrawn for cleaning.

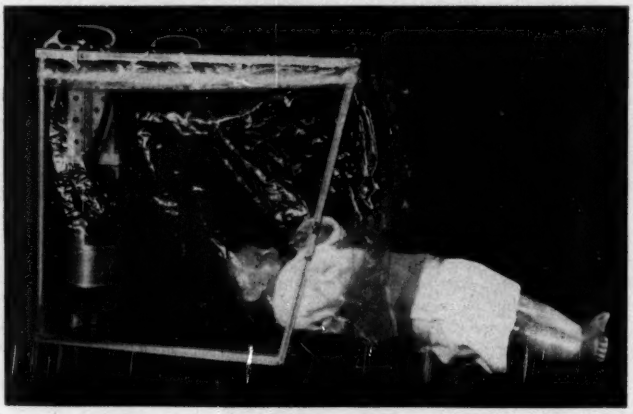

Fig. 2.—Metal mist generator (Mist$O_2$ Gen nebulizer) in place in modified open-top oxygen tent. Nebulizer is suspended from the ice cooler beyond the reach of the patient and may be quickly removed for refilling of the reservoir.

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3. Abramson, H. A.: Principles and Practice of Aerosol Therapy of the Lungs and Bronchi, Ann. Allergy **4**:440, 1946.

The nebulizer is suspended from the ice cooler in one of the corners of a Collins Oxygen Tent [4] (Fig. 2) above the patient's head and beyond his reach. It is connected by means of a thick-walled pressure hose to the flow gauge [5] of the oxygen tank. In operation the flow of oxygen into the nebulizer generates a cloud of mist which billows from the outlet and fills the tent with a dense mist within four to eight minutes. To facilitate concentration of the mist, the top of the tent is partially covered during the first 15 to 20 min. of operation. The density varies directly with the volume of oxygen flowing through the nebulizer. The temperature of the enclosed supersaturated atmosphere is controlled by addition of ice cubes to the cooler in the tent.

Using a Beckman Oxygen Analyzer, oxygen concentrations above 70 vol. %, at a flow of 6 to 8 liters a minute, are consistently obtained.

The entire unit, with the exception of the plastic tent and oxygen tubing, can be dismantled and sterilized in an autoclave.

## SOLUTIONS

In the original work with this form of therapy [1] distilled water alone was nebulized. Subsequent work disclosed that more rapid clinical response was gained

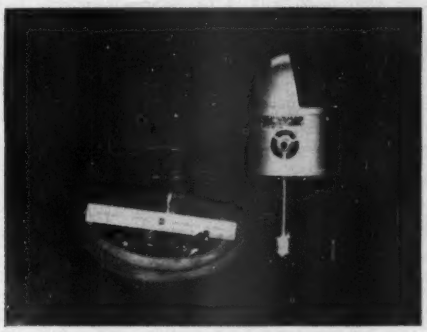

Fig. 3.—Disassembled nebulizer.

when an agent was added which lowered the vapor pressure of the individual droplet. A 5% concentration of glycerin or of propylene glycol was used. Abramson [3] showed that these agents prolonged the life period of the individual droplet and that as a result the mist was more stable and penetrated the respiratory tree more extensively. Our present basic solution consists of a distilled-water base containing 2.5% glycerin, 2.5% propylene glycol, and 0.07% ephedrine alkaloid. In the majority of cases edema of the mucous membranes secondary to inflammation makes use of a shrinking agent desirable. When local high concentrations of anti-

4. Denton, R.: Adaptation of the Burgess Oxygen Tent for Infants, J. A. M. A. **142**:805 (March 18) 1950; Further Modification of the Burgess Open-Top Oxygen Tent for Children, to be published.

5. Bourdon, dial type, gauge is recommended to allow for adequate oxygen flow. The Thorp tube flowmeter when used with this type of nebulizing equipment gives inaccurate readings and will not allow flows above 8 l. a minute.

biotic agents are indicated, penicillin (50,000 to 500,000 units per 100 cc. of solution) or streptomycin (50 mg. to 1 gm. per 100 cc.) have been used. These solutions nebulize to form a fine, dense mist in the open-top tent.

## DISEASES TREATED

A clinical study is in progress on patients whose treatment was chiefly cold humidification. The following case summaries are presented to illustrate responses to this therapy.

*Laryngotracheobronchitis.*—R. W., a 2-mo.-old white boy, was admitted on Jan. 29, 1951, with a four-day history of nasal discharge and cough without febrile response. Three days before admission progressive dyspnea and choking episodes developed.

Physical findings on admission included temperature 99.2 F., pulse rate 140 and respiratory rate 40; he was an acutely ill infant with rapid, noisy respirations, a harsh croupy cough, profuse nasal discharge, diffuse injection of the throat, circumoral cyanosis, and inspiratory subcostal retraction. Percussion showed no abnormalities, and coarse rhonchi were transmitted throughout both lung fields.

Laboratory data were white blood cells 14,500, polymorphonuclear leucocytes 14%, lymphocytes 85%, monocytes 1%. Throat culture revealed moderate growth of coliform bacillus and nonhemolytic Staphylococcus aureus.

Treatment consisted in cold humidification, parenteral administration of antibiotics, and supportive therapy. Response was observed by the second hospital day; only on crying were respirations labored; the harsh cough persisted until the fourth hospital day. The infant was removed from the tent on the third hospital day after 60 hr. of therapy. By the eighth hospital day he was asymptomatic, and physical examination was negative.

*Bronchiolitis and Atelectasis.*—G. W., a 3-mo.-old Negro boy, after 14 days of hospitalization for severe diarrhea, had sudden onset of cough, dyspnea, and expiratory wheezing, with progressive course to severe bronchiolitis within eight hours.

Physical findings included a temperature of 99 F.; the infant was in acute respiratory distress; there were an audible expiratory wheeze and moderately severe suprasternal and subcostal retraction; the chest was hyperresonant to percussion, with definite increase in the anteroposterior diameter; breath sounds were equal bilaterally, and fine crepitant rales were heard at the right base posteriorly.

Chest roentgenograms taken on Feb. 20, 1951 were essentially normal. On the day of onset of respiratory symptoms, repeat roentgen examinations revealed atelectasis of the apical segment of the upper lobe of the right lung and of the lingula of the upper lobe of the left lung.

The infant was started on continuous oxygen-aerosol therapy containing aminophylline on Feb. 26. There was no clinical improvement 30 hr. later, on Feb. 27; the respiratory rate at this time was 68, with expiratory wheezing throughout. By Feb. 28 there was definite clinical improvement, with normal pulse and respirations. Repeat chest roentgenograms showed complete clearing of the atelectasis of the upper lobe of the right lung and almost complete clearing of the lingula of the upper lobe of the left lung; there was some residual emphysema. On March 1, the cold humidification treatment was discontinued and the patient given penicillin aerosol intermittently. A throat culture on Feb. 28 showed a heavy growth of hemolytic Staph. aureus. On March 9 there was a moderate growth of pneumococci. A repeat chest roentgenogram on March 9 showed an essentially normal chest.

*Pneumonia Secondary to Cystic Fibrosis of the Pancreas.*—D. E., a 4-yr.-old white girl known to have cystic fibrosis of the pancreas, entered the hospital Jan. 18, 1951, with a three-day history of onset of cough and fever becoming progressively severe—and associated with vomiting the night before admission.

On admission the positive physical findings included temperature 102 F. (rectally), pulse rate 130 and respiration rate 34. The patient was a moderately thin, acutely ill child with wasting of extremities, a harsh cough, and increased anteroposterior diameter of the chest. The chest was hyperresonant to percussion; many fine moist rales were heard throughout the lung fields.

Laboratory data were urine clear, white blood cells 11,700, with 79% polymorphonuclear leucocytes, 20% lymphocytes, and 1% monocytes. Throat culture revealed a heavy growth of nonhemolytic Staph. aureus moderately sensitive to 10 units of penicillin. Initial roentgenograms of the chest showed a widespread inflammatory infiltration of both lungs with accentuated hilar shadows.

Therapy during seven days of hospitalization included continuous oxygen-aerosol treatment, with penicillin and streptomycin, and chloramphenicol (chloromycetin®) given orally. By the fourth hospital day the patient was afebrile; the respirations were comfortable as compared with the picture on admission. Rales were heard in both lung fields throughout her hospital stay. The patient was discharged home the eighth hospital day on treatment with aureomycin given orally and aerosol containing penicillin and streptomycin given intermittently.

On the 26th day after discharge, the chest was entirely clear, the cough was gone, and weight gain was satisfactory.

*Asthmatic Bronchitis.*—The patient, a 3-yr.-old white boy, entered on March 17, 1951, with a past history of asthma and a recent upper respiratory tract infection, complicated by a cough of progressive severity for 24 hr. before entry, with associated onset of dyspnea the night before admission.

Admission data included temperature 99.4 F. (rectally), pulse rate 130, and respiratory rate 50. He was a pale child in respiratory distress, with a persistent dry cough; there were an audible expiratory wheeze and coarse expiratory rales heard throughout both lung fields, associated with musical sounds.

Laboratory data were urine clear, white blood cells 15,400, with 8% eosinophiles. Roentgen studies of the chest on March 17 showed accentuation of bronchial shadows.

Treatment during four days of hospitalization included administration of aureomycin orally and penicillin intramuscularly and 48 hr. of continuous oxygen aerosol. By the third hospital day the patient was comfortable when out of the tent; chest examination showed fine inspiratory rales at the left base posteriorly which were almost entirely clear by discharge on March 20, the third hospital day.

## COMMENT

The combination of an adequate supply of oxygen and continuous aerosol therapy offers the patient with certain respiratory infections highly desirable conditions for recovery. It also offers the patient who has undergone tracheotomy a means of maintaining the normal moisture of the respiratory mucous membrane. A supersaturated atmosphere can be provided in a short time within a limited area, and the nebulized particles remain suspended because of their small size. Continuous therapy can be administered to patients not suited to intermittent aerosol therapy.

To date the chief criticism from the attending personnel has been that the nebulized mist is of such density that it obscures the patient from view from the nursing station.

## SUMMARY

A practical means of administering a supersaturated, oxygen-rich atmosphere is reported. By the use of oxygen under pressure, therapeutic solutions are nebulized continuously into a modified Collins Oxygen Tent. Temperature regulation is effi-

cient. With this apparatus the environmental conditions for treating inflammatory and obstructive respiratory diseases approach the optimum.

The atmosphere in the tent contains high levels of oxygen and carries the necessary specific medicaments which penetrate throughout the respiratory tree. The patient is easily accessible, and nursing and other medical care is convenient. These units may be set up in any location in the hospital or the home in adequate numbers to meet seasonal demands.

Dr. Chester M. Weseman, Chief of the Otorhinolaryngology Service, and Dr. Paul C. Samson, Chief of the Thoracic Surgery Service, of the Children's Hospital of the East Bay, Oakland, Calif., gave cooperation and advice in the clinical application of this form of therapy. Mr. Leon Cameto and Mr. L. Robert Cameto, of the Production Foundry Co., Oakland, Calif., developed the Mist$O_2$ Gen.

# Case Reports

## TRICHOBEZOAR AS CAUSE OF INTESTINAL OBSTRUCTION IN A TWO-AND-A-HALF-YEAR-OLD CHILD

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HERBERT SCHREIBER, M.D.
AND
BEATRICE SCOTT, M.D.
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TRICHOBEZOAR without a gastric component as the etiological factor in intestinal obstruction is unusual. Despite its rarity in any age group, this condition should be considered in all cases of intermittent or partial intestinal obstruction. Patients with this condition present a symptom complex which should permit a presumptive preoperative diagnosis.

Bezoars are described as concretions of various foreign or intrinsic substances found in the stomach and the intestines of both man and animal. Those in man have been classified as trichobezoar (hairball), trichophytobezoar (ball of hair and vegetable fiber), phytobezoar (ball of vegetable fiber), and other concretions. Trichobezoar occurs more frequently in females than in males, and most frequently between the ages of 10 and 19 yr.[1]

In a comprehensive review article, DeBakey and Ochsner [1] collected 171 cases of trichobezoar and added one of their own. They found that trichobezoars occurred in 55.3% of 311 reported cases of bezoars. Of 156 cases of trichobezoar, intestinal obstruction developed in 17, or 10.8%. The number of cases of obstruction caused by an intestinal trichobezoar without a hairball in the stomach was not reported.

Since the DeBakey and Ochsner review, MacKeith and Sangster,[2] Harris,[3] and Watt and Harner [4] have reported three additional cases of intestinal obstruction caused by trichobezoars in children. Harris' case, that of a 3-yr.-old child and the youngest previously reported in the literature, emphasizes the peculiar symptomatology which these children present.

### REPORT OF A CASE

M. B., a 2½-yr.-old Negro girl, was admitted to the hospital on Jan. 6, 1950, with a five-day history of intermittent, nonlocalizing, abdominal pain and occasional episodes of vomiting. She had been treated initially by a private physician, who had administered penicillin and sulfadiazine

From the Pediatric and Surgical Services, Harlem Hospital (Morris Gleich, M.D., Director of Pediatrics, and Louis T. Wright, M.D., Director of Surgery).

1. DeBakey, M., and Ochsner, A.: Bezoars and Concretions: A Comprehensive Review of the Literature with an Analysis of 303 Collected Cases and a Presentation of 8 Additional Cases, Surgery **4**:934, 1938; **5**:132, 1939.

2. MacKeith, R. C., and Sangster, A. H.: Trichobezoar (Hairball) Causing Acute Intestinal Obstruction in a Child Aged 3 Years, Arch. Dis. Childhood **14**:356, 1939.

3. Harris, V. C. J.: Unusual Case of Intestinal Obstruction in a Child, Brit. M. J. **2**:754, 1942.

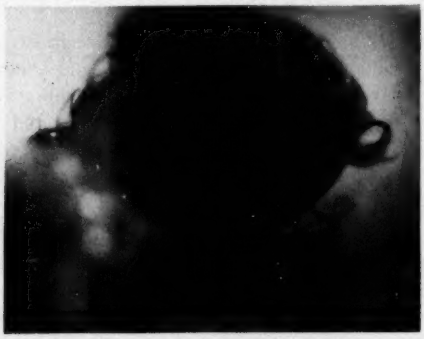
4. Watt, C. H., and Harner, J. W.: Bezoars Causing Acute Intestinal Obstruction, Ann. Surg. **126**:56, 1947.

for tonsillitis. For five days before admission, the patient had experienced obstipation and anorexia. She was brought to the hospital shortly after vomiting a small quantity of blood-streaked material.

The past medical history was significant in that the child had had a poor appetite since the age of 1 year, and she had lost 12 lb. (5.4 kg.) in the three months prior to admission. The remainder of the review of systems and the family history were noncontributory.

On admission to the hospital, the rectal temperature was 37.5 C. (99.5 F.), the respiratory rate was 20 per minute, the pulse rate was 114 per minute, and the weight was 12.3 kg. Physical examination revealed a markedly dehydrated, chronically ill child in no acute distress. The abdomen was protuberant, soft, and tympanitic. There was slight tenderness in the right lower quadrant. Bowel sounds were audible, and no masses were palpable. The child had a full head of hair. The remainder of the examination was normal.

The leucocyte count was 15,000 per cubic millimeter, with 64% polymorphonuclear cells, 32% lymphocytes, 3% monocytes, and 1% eosinophils. The erythrocyte count was 4,600,000 per cubic millimeter, with 14.9 gm. of hemoglobin (Sahli). The sickle cell preparation was negative. The urine was normal except for the presence of acetone. The Kahn reaction of the blood and a Mantoux test with 0.01 mg. of old tuberculin were negative.



Hairball.

During the next few hours, the patient had occasional episodes of intermittent, nonlocalizing, abdominal pain. She passed neither stool nor flatus. When given an ounce (30 cc.) of water, she vomited immediately.

Approximately 10 hours after admission, the temperature was 37.8 C. (100 F.) and the pulse rate 114 per minute. The abdomen was slightly distended, with voluntary guarding on the right side and tenderness on deep palpation in the right lower quadrant, without any masses. Bowel sounds and visible peristalsis were absent. Rectal examination revealed no abnormalities. The patient was given a low saline enema, which produced a small amount of brownish, blood-streaked stool without flatus. Again, when an ounce of water was given orally the patient vomited immediately.

Roentgenograms of the patient taken in supine and upright positions were interpreted as normal.

In view of the vomiting, obstipation, progressive distention, and recurrent, intermittent, nonlocalizing, abdominal pain, and despite the fact that the patient did not appear acutely obstructed, intestinal obstruction was considered probable, and surgical exploration was, therefore, warranted.

The patient was prepared preoperatively with antibiotics, fluids by parenteral method, and Wangensteen suction. A laparotomy was performed, with the patient under ether anesthesia. A small amount of clear fluid was found in the peritoneal cavity. Two compressible masses, each measuring about 3 by 2.5 cm., were palpated in the terminal ileum. The bowel proximal to the masses was distended, and the bowel distal to the masses was partially collapsed. The

masses were manually compressed, and they passed readily through the ileocecal valve into the cecum. There were no masses in the stomach, and the remainder of the intestinal tract was normal.

In response to direct questioning after the operation, the mother remembered an incident about 10 mo. previously when the child had been hospitalized at another institution for acute tonsillitis. At the time of the child's discharge the mother had been surprised by the sparsity of head hair, which had a peculiar patchy distribution. The mother also recalled that at another time, while the child was being cared for in a nursery for several months, she had been seen rubbing her hair frequently, but no trichophagia had been noted.

The postoperative course was uneventful. The patient passed the first hair-containing stool on the third day (Figure). The subsequent three stools also contained matted hair. Twelve days after the operation a gastrointestinal series revealed normal bowel patterns. No masses were seen.

## COMMENT

The case presented is notable because of the absence of a hairball in the stomach, which is usually found in this peculiar condition. To date our 2½-yr.-old patient is the youngest with intestinal obstruction due to trichobezoars reported in the literature.

The following four important points in diagnosis were demonstrated by this case: 1. There was a prolonged history of abdominal complaints. 2. There were signs of partial intestinal obstruction. 3. The patient appeared chronically rather than acutely ill, despite the history. 4. The temperature was low grade, and the pulse rate only slightly increased.

The clinical picture described is apparently typical of hairball obstruction, for all the cases dealing with children reported in the literature have followed essentially the same pattern. Although intestinal obstruction was recognized as a strong possibility in this case, the acuteness of the problem was masked by the intermittency of the attacks, and by the long-standing history elicited. Knowledge of this pattern should prevent any unnecessary delay in surgical intervention.

## SUMMARY

A case of intestinal obstruction caused by trichobezoars without a gastric component in a 2½-yr.-old child is presented.

A clinical picture is described which appears to be typical of hairball obstruction, and which should be considered in the differential diagnosis of intestinal obstruction in children.

441 West End Ave. (24)

# RETROCAVAL URETER

## Report of Two Cases Diagnosed Preoperatively in Childhood

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AND
WILLIAM E. CHASE, M.D.
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SINCE the original report of retrocaval ureter in 1893, 44 cases have been reported in the literature. Twenty-two of these cases were diagnosed post mortem, and eight cases were diagnosed preoperatively. Only one case in childhood has been previously reported,[1] and this was the case of a 12-yr.old girl. The two following case reports raise the total number of cases diagnosed in childhood to three and are of the youngest patients described. We have seen three cases during the past two years, but one case was of an adult and is not included in this report. It would appear that familiarity with the condition as a cause of right ureteral obstruction is important in determining the incidence of its recognition.

This congenital anomaly consists of an abnormal course of the right ureter and is synonymously referred to as postcaval or circumcaval ureter. Instead of descending lateral to the inferior vena cava, the right ureter passes behind and encircles the vena cava and then pursues its normal course into the pelvis (see Fig. 1*A*). At the point where the ureter passes behind the vena cava it is partially obstructed, and this incomplete obstruction results in dilatation of the ureter proximal to this point and of the renal pelvis. For a more detailed description of this condition, the embryological malformations resulting in this anomaly, and the recommended surgical techniques for repair of the malformation, one is referred to Heslin and Mamonas' review of the literature.[2] The diagnosis should be thought of in all cases of isolated right-sided hydronephrosis, especially in children. The roentgenographic features of dilatation of the renal pelvis and proximal ureter on the right side, deviation of the right ureter to the midline in its midportion, and the normal caliber of the distal portion of the right ureter are pathognomonic of retrocaval ureter (see Fig. 1*B*). There is nothing in the history or on physical or cystoscopic examination that is diagnostic. The symptoms vary from none to renal colic, and intermittent hematuria is a frequent finding. Since the condition is amenable to corrective surgical measures, it is important from a practical standpoint not to overlook the diagnosis.

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From the Department of Radiology (Dr. Parks) and the Brady Institute of Urology (Dr. Chase), Johns Hopkins Hospital.

1. Creevy, C. D.: Recognition and Surgical Correction of Retrocaval Ureter: Case Report, J. Urol. **60**:26-30, 1948.

2. Heslin, J. E., and Mamonas, C.: Retrocaval Ureter: Report of 4 Cases and a Review of the Literature, J. Urol. **65**:212-222, 1951.

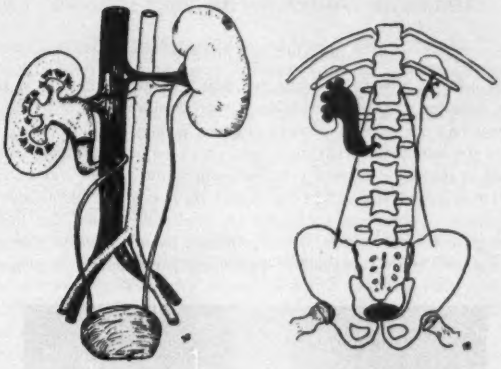


Fig. 1.—Retrocaval ureter. *A*, a drawing showing the right ureter passing behind and around the vena cava. *B*, a drawing of the urographic findings depicting the dilated renal pelvis and proximal ureter with deviation of the proximal ureter to the midline in a hook-like fashion. The normal distal ureter is not shown because this drawing represents the findings seen on an excretory urogram.

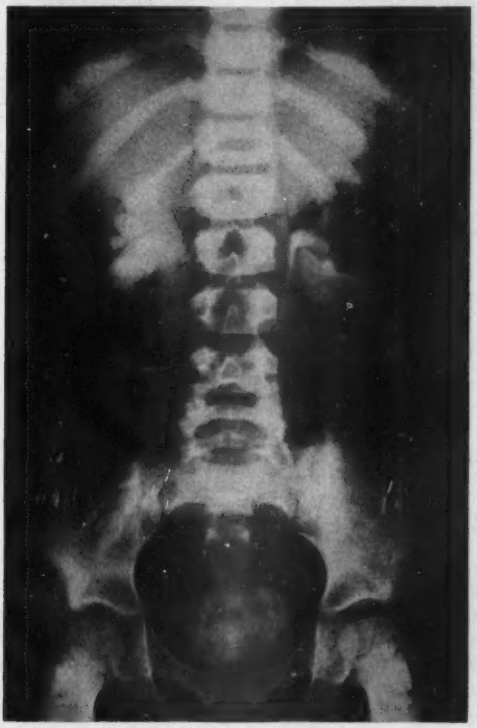

Fig. 2 (Case 1).—Excretory urogram 10 min. following intravenous injection. Figure 1*B* is a drawing of this film.

REPORT OF CASES

CASE 1 (Fig. 2).—B. G., a 6-yr.-old white boy, was admitted to the Johns Hopkins Hospital because of gross hematuria. The past history was irrelevant. About two months before admission the patient had one episode of painless gross hematuria. On the day of admission the patient was seen in the outpatient department because of earache and abdominal pain. Because a routine urinalysis at that time showed gross hematuria, the patient was admitted. Results of physical examination were normal except for a dull right eardrum membrane and slight right costophrenic tenderness. There was no edema or hypertension, and the fundi were normal. Laboratory studies gave normal results. Roentgenologic examinations of the abdomen, sinuses, and mastoids did not reveal any evidence of pathologic involvement. Repeated urine cultures

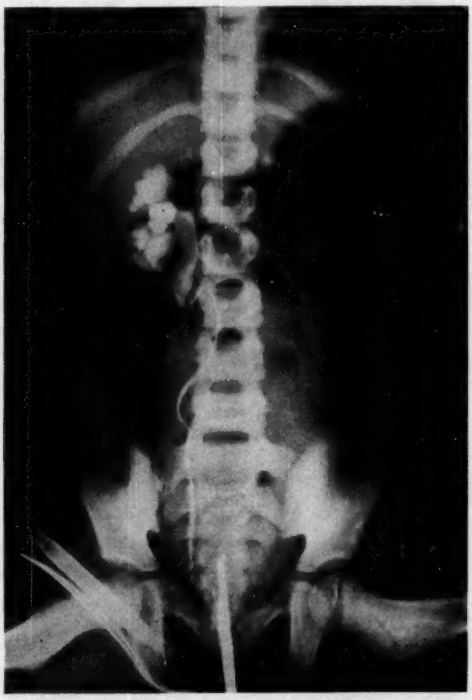

Fig. 3 (Case 2).—Retrograde urogram on right side confirming the excretory urographic findings, which were similar to those shown in Case 1.

were negative, and no crystalluria was noted. On the third hospital day the urine was normal, except for a rare red blood cell on microscopic examination of the sediment. An excretory urogram was performed on the 10th hospital day, and the films were interpreted as showing obstruction of the proximal third of the right ureter with right hydronephrosis due to retrocaval ureter. On the 13th hospital day, the patient was taken to surgery, and the right kidney and ureter were exposed through a right flank incision. At a point about 10 cm. below the renal pelvis, the ureter was found to pass posterior to and then around the vena cava to descend in a normal position. The ureter below the retrocaval portion was normal in caliber. The ureter was dissected free, and then the pelvis was circumferentially incised at a point 1 cm. above the ureteropelvic junction. The ureter was easily unwound from the vena cava and placed in a normal position. The ureter was then reanastomosed to the kidney pelvis, and temporary

pyelostomy drainage and ureteral splinting were established with catheters. The patient tolerated the procedure well. After the operation administration of aureomycin and penicillin was instituted, and the postoperative course was uneventful. On the eighth postoperative day the sutures were removed, and on the 14th postoperative day the pyelostomy-drainage tube and the ureteral catheter were removed after pyelostomy injection showed the right ureter to be patent. An excretory urogram performed one month after operation showed the right ureter to be in a normal position without evidence of obstruction, although slight residual dilatation of the right renal pelvis was still evident.

CASE 2 (Fig. 3).—This was the first Johns Hopkins Hospital admission of A. S., a 5-yr.-old white boy, who was admitted for repair of a congenital hypospadias. The family and past history was not remarkable, except for repair of a left inguinal hernia at the age of 2 yr. He had never had any difficulty voiding, nor were hematuria, pyuria, or lithuria ever present. A review of the systems gave normal results. Physical examination showed no abnormality except for a well-healed left herniorrhaphy scar, an infantile penis with a definite ventral curve (chordee) and a ventral meatus, 1 cm. proximal to the glans penis. Congenital absence of the terminal portion of the distal phalanx of the left little finger was noted. The urine was normal. The patient was admitted for plastic repair of the penis, and prior to the operation a routine excretory urogram was made. The urogram showed a normal left upper urinary tract. The right pelvis and proximal one-third of the right ureter were dilated, and the ureter deviated sharply toward the midline at the level of the obstruction. A diagnosis of retrocaval ureter was made. To confirm the diagnosis, retrograde pyelography was performed on the right side, and the pyelograms were considered pathognomonic of retrocaval ureter. After the retrograde studies, the patient exhibited high fever, vomited, and complained of pain over the right kidney. On the third day after retrograde studies, the fever was spiking, the urine was loaded with white blood cells, and blood and urine cultures were reported as containing Pseudomonas aeruginosa. The patient was acutely ill and had to be placed in an oxygen tent. Because the response to antibiotic therapy was unfavorable, an emergency right nephrectomy was performed on the fifth day after the retrograde studies. At operation acute suppurative pyelonephritis, with numerous abscesses studding the cortex of the kidney, was encountered, and no urine could be obtained from the kidney pelvis at operation. Because of the critical condition of the patient, the right ureter was not explored to confirm the diagnosis of retrocaval ureter. After the operation the patient rapidly recovered and on the fourth postoperative day was afebrile. The patient was discharged on the 16th postoperative day to be followed in the outpatient department. He has been followed for the past six months without evidence of urinary-tract infection.

## COMMENT AND CONCLUSIONS

Two cases of retrocaval ureter in childhood are reported. Both cases were diagnosed prior to surgical intervention. One case was diagnosed by excretory urography alone and proved on operation. The other case was diagnosed by excretory urography and confirmed by retrograde urography. After the retrograde urogram was made, the patient had acute suppurative pyelonephritis, requiring an emergency right nephrectomy; because of the condition of the patient, the right ureter was not explored to gain surgical confirmation of the malformation. The urographic evidence of the retrocaval ureter was sufficient to warrant the diagnosis beyond question. These two cases are added to the total of 44 cases of retrocaval ureter reported, and they bring the total number of cases recognized in childhood to three. Familiarity with the condition will result in the more frequent recognition of the anomaly and, with corrective surgical treatment, in the prevention of chronic hydronephrosis. The urographic findings are characteristic. In every case of right-sided hydronephrosis, retrocaval ureter should be considered in the differential diagnosis, especially if the patient manifests other congenital anomalies.

# CYSTINOSIS (CYSTINE-STORAGE DISEASE)

## Report of a Case with Chemical Isolation and Quantitative Determination of Cystine in Lymph Nodes, Spleen, and Liver

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AND
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ATLANTA

CYSTINOSIS is an unusual disorder in which cystine crystals are deposited throughout the body, especially in the cells of the reticuloendothelial system. Twenty cases have been reported in the literature, 16 of which were studied by autopsy. The disease has been briefly mentioned in the literature on "resistant rickets," cystinuria, and the Fanconi syndrome. Only two cases have been reported from this country.[1] The literature prior to 1943 has been reviewed by McCune and others[2] and has been recently summarized by Rapaport[3] and Freudenberg.[4]

Cystinosis was first described by Abderhalden and Kaufmann, cited by McCune and others,[2] in 1903. Lignac[5] observed the second case in 1924. Since 1940 eleven cases have been recorded, and in eight of these the diagnosis was made clinically. The disease has been studied extensively in Europe by Fanconi and Bickel[6] and Hottinger[7] but apparently has not been recognized clinically in this country.

The case report of the following patient is presented because, in retrospect, his clinical manifestation and course were quite typical of cystinosis and quantitative recovery of cystine from the tissues was performed.

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From the Departments of Pathology, Emory University School of Medicine, Emory University and Grady Memorial Hospital.

1. Clarke, B. E., and Jackson, H. F.: Cystinosis: A Report of Two Cases with Postmortem Examination, Am. J. Path. **26**:726, 1950.

2. McCune, D. J.; Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (the Fanconi Syndrome): Report of a Case in Which Increased Urinary Organic Acids Were Detected and Identified with a Review of the Literature, Am. J. Dis. Child. **65**:81 (Jan.) 1943.

3. Rapaport, M.: Inborn Errors of Metabolism: Cystinuria, in Nelson, W. E.: Textbook of Pediatrics, ed. 5, Philadelphia, W. B. Saunders Company, 1950, pp. 288-291.

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5. Lignac, G. O. E.: Über Störung des Cystinstoffwechsels bei Kindern, Deutsches Arch. klin. Med. **145**:139, 1924.

6. (*a*) Fanconi, G.: Weitere Beiträge zur Cystinkrankheit (der Amindiabetes), Helvet. paediat. acta **1**:183, 1946. (*b*) Fanconi, G., and Bickel, H.: Die chronische Aminoacidurie (Aminosaürediabetes oder nephrotischglukosurischer Zwergwuchs) bei der Glykogenose und der Cystinkrankheit, ibid. **4**:359, 1949.

7. Hottinger, A.: Über Cystin-Diathese, Ann. paediat. **156**:257, 1941.

REPORT OF CASE

*First Hospital Admission.*—A 19-mo.-old white male infant entered another hospital on Jan. 7, 1949, because of repeated vomiting and constipation for 11 mo.

The patient was delivered at term, weighing 8 lb. 7 oz. (3,827.19 gm.). For six months he was breast-fed and developed normally. At the age of 3 mo. the feeding of solid foods was started, but no cod-liver oil or orange juice was given. He had received no immunizations. At the age of 6 mo., when he weighed 22 lb. (9,979.02 gm.), frequent episodes of anorexia, vomiting, polyuria, fever, and constipation appeared. He was weaned and given whole boiled cow's milk and other liquids. At the onset of his illness solid foods were accepted only to be spit out. Later solid foods were refused altogether, but he continued to take liquids orally. Fluid intake and urine output were thought to be excessive. There was a progressive loss of weight. Constipation became increasingly troublesome. About once a month the symptoms became worse for four to seven days and were characterized by vomiting, fever, polyuria, and dehydration.

On admission to the hospital the patient weighed 15 lb. 3 oz. (6,888.93 gm.). He was emaciated, dehydrated, pale, and irritable; otherwise, the results of physical examination were not remarkable. There was no enlargement of the epiphyses or costochondral junction. The blood-cell counts and stained blood smear were normal. On 34 analyses the specific gravity of

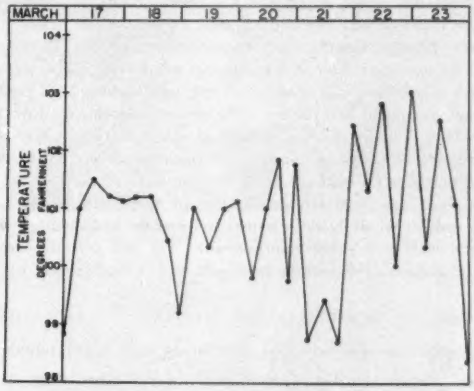


Fig. 1.—Typical temperature curve for one week showing the high remittent fever.

the urine ranged from 1.006 to 1.020. The reaction varied from "acid" to "alkaline." Albumin was constantly present in amounts designated as a "trace" to "one plus." Qualitative Benedict's tests for sugar were consistently negative. A few unidentified crystals were noted on each urinalysis. A phenolsulfonphthalein test, in which only 15 cc. of urine were collected, showed 35% excretion in two hours. The results of the serologic test for syphilis were negative. The stool contained pancreatic enzymes (trypsin) but no fatty acids, neutral fats, blood, ova, or parasites. The serum albumin was 6.0 gm., the serum globulin 1.4 gm., and the blood nonprotein nitrogen 35 mg. per 100 cc. A single-serum calcium determination was 9.5 mg. per 100 cc. A serum-phosphorus determination was not obtained. The fasting blood sugar was 95 mg. per 100 cc., and the serum sodium was 144 mEq. per liter. Blood and stool cultures as well as agglutinations for Brucella, typhoid "O" and "H," and paratyphoid "A" and "B" were negative.

The patient's temperature ranged throughout this hospital stay from 100 F. to 104 F., despite adequate hydration and treatment with penicillin and sulfadiazine (Fig. 1). His appetite remained poor. Vitamins A, B complex, C, and D were given. The fluid intake and urine output were excessive; the stools were large and hard. Two weeks after admission he weighed 13 lb. (5,896.69 gm.). Because of the lack of vitamin A absorption (after administration of 1.4 cc. of percomorph liver oil [oleum percomorphum®] orally), pancreatic extract was given daily for three months without improvement. The diet was supplemented with protein hydrolysates.

An excretory urogram showed dilated ureters, and later a constriction in the posterior urethra was demonstrated by the passage of a sound. Repeated urethral dilatations were necessary to permit the insertion of the cystoscope. Retrograde pyelograms revealed bilateral segmental dilatation of the ureters without evidence of ureteral obstruction or abnormality of the bladder. Roentgenograms of the chest and extremities showed scurvy and rickets.

The patient improved slowly and was discharged on August 19, without a definite diagnosis, after eight months of hospitalization, weighing 16 lb. 12 oz. (7,597.67 gm.). Supplemental protein hydrolysates and a laxative diet were prescribed. Following discharge, combined immunization for diphtheria, pertussis, and tetanus were given. His condition remained unchanged for eight months, with a weight loss of 9 oz. (255.15 gm.). There followed a period of improvement lasting for several months.

In June, 1950, he developed whooping cough; vomiting recurred and his weight decreased to 11 lb. (4,989.51 gm.). On July 11 he was admitted to Grady Memorial Hospital.

*Second Hospital Admission.*—The patient's temperature was 101.8 F., the pulse 100 a minute, and the blood pressure 80 systolic and 40 diastolic. The child was extremely dehydrated. A few rales were heard in the posterior lung fields. The bladder was distended. No skeletal deformities were noted. The erythrocytes numbered 3,500,000 and the leucocytes 21,000 per cubic millimeter of blood. On a stained blood smear there were 58% neutrophiles and 40% lymphocytes. The urine had a pH of 7.5 and a specific gravity of 1.008. The results of the test for albumin were negative and of the qualitative Benedict's test 1 plus. A few leucocytes were seen in the centrifuged sediment. The nonprotein nitrogen on the day of admission was 110 mg. per 100 cc. Three days later it was 90 mg. per 100 cc. The serum protein was 5.7 gm. per 100 cc. The spinal fluid was clear, colorless, and contained 15 erythrocytes per cubic millimeter and 99 mg. of protein per 100 cm. The serum chlorides on July 11 were 67.8 mEq. per liter. On July 14 the serum sodium, potassium, and chlorides were 144.5, 4.8, and 77.4 mEq. per liter respectively. Two blood cultures were negative. The chest roentgenogram showed some streaky infiltration, but no evidence of rickets or scurvy was seen.

The patient was given large intravenous infusions of dextrose in water and isotonic sodium chloride solution as well as whole blood, plasma, and protein hydrolysates. Feeding by gavage was attempted; there was only slight improvement. On the seventh hospital day suddenly dyspnea, cyanosis, and abdominal distention developed, and he died several hours later.

## METHODS OF DEMONSTRATING CYSTINE IN THE TISSUES

Following autopsy the diagnosis of cystinosis was established.

*Chemical Studies.*—Three samples of fresh-frozen tissue were available for the isolation experiments: liver, 37.4 gm.; spleen, 4.5 gm.; and lymph nodes, 0.147 gm. Each sample was cut into small pieces with scissors and then homogenized in a Ten Broeck grinder with a volume of 10% trichloroacetic acid equal to the weight of tissue taken. The mixture was centrifuged, the supernatant fluid was decanted, and the residue was extracted twice with half the volume of 10% trichloroacetic acid. The supernatant fluids after centrifugation were combined and heated at a gentle boil on the hot plate until the pH of the mixture was about four, indicating that most of the trichloroacetic acid had been decomposed. The solution, which had been concentrated to less than half the original volume during the heating, was chilled in the refrigerator, whereupon a crystalline precipitate formed within a few minutes. With the spleen and lymph-node samples crystallization occurred from the hot, weakly acid solution. In each instance, the crystals, on microscopic examination, proved to be the highly transparent hexagonal plates and prisms characteristic of cystine (Fig. 2). An additional crop of crystals was obtained by evaporating the first supernatant liquids to dryness *in vacuo* and extracting the dry residues with dilute ammonia. When these extracts were acidified with acetic acid (pH 4 to 5) and chilled, more cystine crystallized.[8]

The combined lots of crystals from each tissue were twice recrystallized from dilute ammonia made slightly acid with acetic acid, dried *in vacuo*, and weighed. The respective yields were: from the liver, 33.7 mg. (0.09%); from the spleen, 40.6 mg. (0.09%); and from

8. Dr. Evangeline Papageorge and Dr. Alfred E. Wilhelmi and Miss Phyllis Strobel, of the Department of Biochemistry of Emory University School of Medicine, Emory University, carried out the isolation and identification of cystine from the tissue samples.

the lymph nodes, 3.2 mg. (2.18%). The crystalline material from these tissues gave a strong nitroprusside reaction after, but not before, treatment with cyanide. The results of the labile sulfur test were strongly positive. The formation of characteristic crystals of cystine phosphotungstate on a microscope slide, as described by Bulloch and Kirk,[9] was observed (Fig. 3). The dibenzoyl derivative was in the course of preparation at the time this paper was written.

*Histological Studies.*—All tissues were fixed in Zenker's fluid with 5% glacial acetic acid and 10% formaldehyde solution U. S. P. (formalin®). In addition, unfixed slices of spleen, lymph nodes, and liver were stored in the deep freezer. Sections from all tissues were stained with hematoxylin and phloxine. The following special stains were used: Mallory's aniline blue

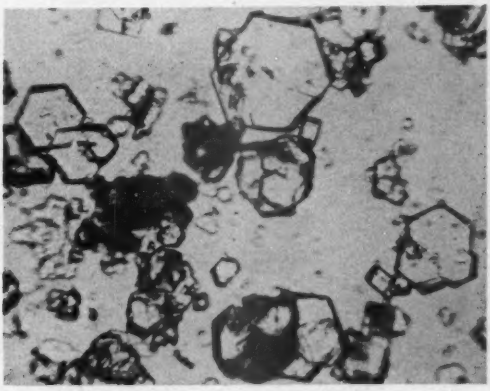

Fig. 2.—Cystine crystals isolated from spleen and lymph nodes; × 210.

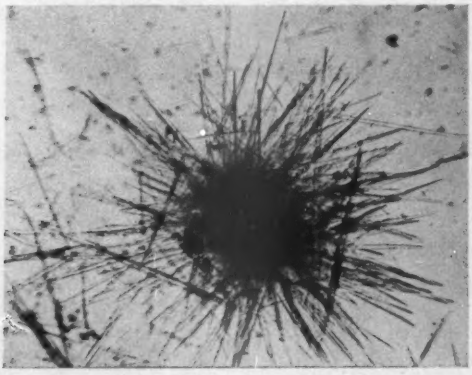

Fig. 3.—Cystine phosphotungstate crystals; × 210.

stain, Kóssa's stain for calcium, scarlet red, and iron stain. Since cystine is dissolved in aqueous solutions, blocks of the frozen tissue were fixed at a later date in 95% alcohol, embedded in paraffin, and stained with 0.5 toluidine blue in 20% alcoholic solution.[10] Frozen sections on unfixed tissues were also prepared and stained by Giemsa's method. The addition

9. Bulloch, B., and Kirk, G. F.: Microscopy of the Amino-Acids and Their Compounds: I. Phosphotungstates and Phosphomolybdates, Mikrochemie **18**:129, 1935.

10. Russell, D. S., and Barrie, H. J.: Storage of Cystine in Reticulo-Endothelial System and Its Association with Chronic Nephritis and Renal Rickets, Lancet **2**:899, 1936.

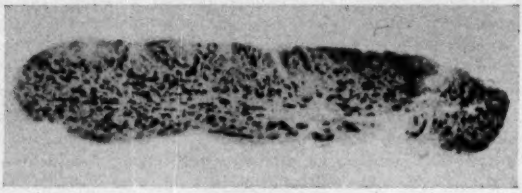

Fig. 4.—Mesenteric lymph node. The black deposits are cystine crystals. Toluidine blue stain; × 9.

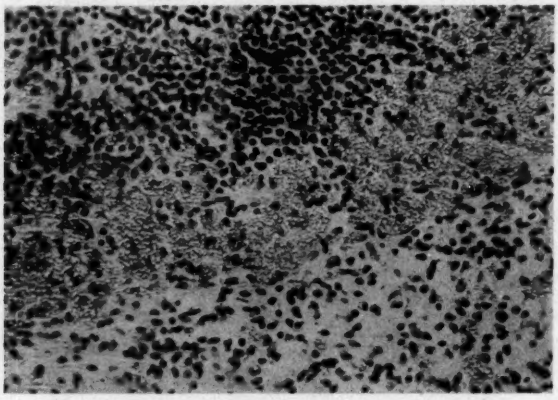

Fig. 5.—Spleen, with extensive cystine crystals. Note that the red pulp is more involved than are the follicles. Toluidine blue stain; × 210.

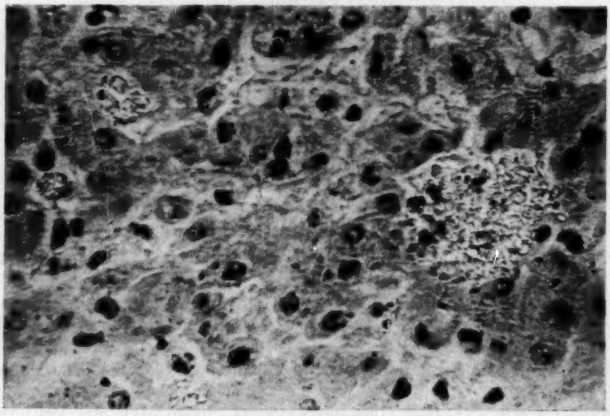

Fig. 6.—Liver with cystine crystals. On the left several Kupffer cells containing crystals are seen. A large deposit is present on the right. Toluidine blue stain; × 840.

of a few drops of concentrated hydrochloric acid to paraffin sections containing cystine crystals produced the long needles of cystine hydrochloride.[10] Sections containing crystals were also examined under polarized light.

*Gross Findings at Autopsy.*—The autopsy was performed seven hours post mortem. The body measured 72 cm. in length. Dehydration and inanition were present. The mesenteric lymph nodes were prominent and on a cut surface appeared sprinkled with minute amounts of whitish crystalline material. The small spleen (17.5 gm.) showed similar, but less marked, changes on a cut surface. Both ureters were markedly dilated with slight bilateral hydro-

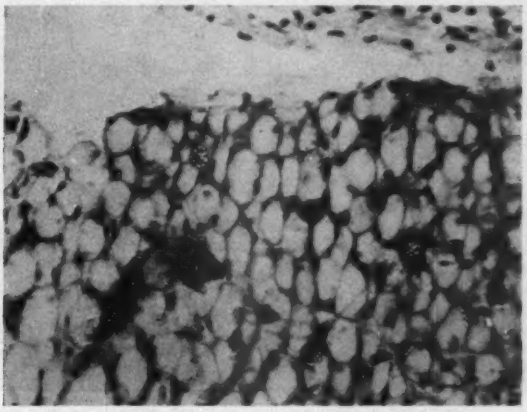

Fig. 7.—Mesenteric adipose tissue with cystine crystals in the fixed-connective tissue elements. Frozen section, Giemsa stain; × 420.

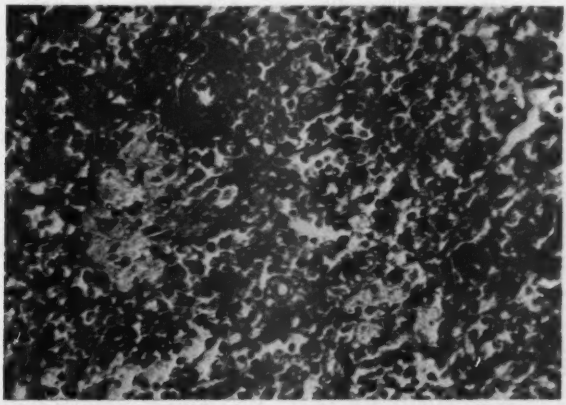

Fig. 8.—Spleen showing two collections of large mononuclear cells with reticulated cytoplasm. The cystine crystals have been dissolved during fixation in Zenker's fluid. Mallory's aniline blue stain; × 420.

nephrosis. The kidneys (combined weight 100 gm.) were not remarkable. The bladder was distended with 500 cc. of clear urine. In the posterior urethra ridges consistent with previously dilated valves were seen. The lungs showed patchy atelectasis. The adrenals (combined weight 2.5 gm.) appeared normal. A complete autopsy revealed no other gross findings.

Postmortem cultures from the heart blood yielded no growth. Cultures of the lungs grew organisms of the Chromobacterium group.

*Histological Observations.*—In alcohol-fixed or frozen sections the mesenteric lymph nodes and to a lesser degree the spleen and liver contained large numbers of crystals, which were small, flat, and hexagonal or rectangular or amorphous in shape. They were either colorless or light yellow-brown and appeared doubly refractile under polarized light. In the lymph nodes and spleen the crystals were diffusely distributed, but the follicles were less involved (Figs. 4 and 5). Most of the crystals appeared to be within large mononuclear cells, although some were noted extracellularly. In the liver, the crystals were present in the prominent Kupffer cells and in the connective tissue of the portal spaces (Fig. 6). Some crystals were also noted

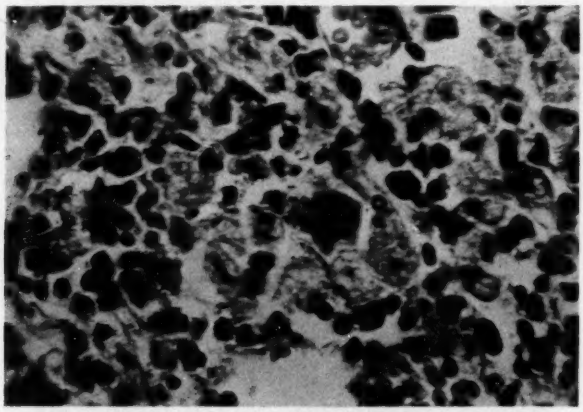

Fig. 9.—Bone marrow fixed in Zenker's fluid showing many large mononuclear cells with reticulated cytoplasm. Hematoxylin and phloxine stain; × 840.

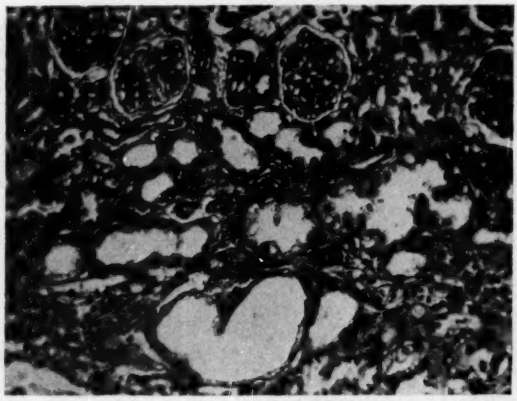

Fig. 10.—Kidney fixed in Zenker's fluid. Note distention of tubules and cytoplasmic vacuolization of the tubular epithelium. Hematoxylin and phloxine stain; × 210.

in the fixed-connective tissue elements of the mesenteric fat surrounding the lymph nodes (Fig. 7). Conversion of these crystals to long needles following addition of strong hydrochloric acid as described above was readily accomplished.

In sections fixed with either Zenker's fluid or formaldehyde solution U. S. P. the cystine crystals had disappeared, but their location was marked by collections of large mononuclear cells with reticulated or finely vacuolated cytoplasm. These cells were well demonstrated with

Mallory's aniline blue stain (Fig. 8). The cytoplasmic vacuoles did not react with fat or iron stains, but some contained minute amounts of material reacting with Kóssa's silver nitrate stain. Similar vacuolated cells were numerous in the bone marrow (Fig. 9), and a few could also be found in the interstitial connective tissue of the pancreas. Cells of this appearance were not found in the remaining tissues.

The kidneys failed to show cystine deposits, but unfixed-frozen or alcohol-fixed material was not available. Extensive changes involving the proximal convoluted tubules and to a lesser extent the distal convoluted tubules as well as the ascending portions of Henle's loop characterized the renal lesion (Fig. 10). These changes ranged from slight to marked cytoplasmic vacuolization to actual necrosis of the epithelial cells. Lipid material could be demonstrated in some but not in all of the vacuoles. The tubular and to a lesser degree the glomerular basement membranes were slightly thickened. The glomeruli appeared normal. An occasional arteriole displayed slight concentric medial thickening. The interstitial connective tissue was normal in amount and distribution without any collections of large mononuclear cells consistent with cystine deposits. Enchondral bone formation as seen at the costochondral junction was arrested, but there was no evidence of either rickets or scurvy.

Incidental findings were a diffuse interstitial pneumonitis, secondary hyperplasia of the bone marrow, dilatation of the pancreatic acini, and lipoid depletion with minimal focal necrosis of the adrenal cortex.

*Anatomic Diagnosis.*—The diagnosis was cystinosis (cystine-storage disease) with involvement of liver, spleen, bone marrow, lymph nodes, mesenteric fat, and pancreas; tubular nephritis associated with cystinosis; arrest of bone growth; interstitial pneumonitis; lipoid depletion and focal necrosis of adrenal cortex; secondary hyperplasia of bone marrow; marked megaloureter and slight, bilateral hydronephrosis secondary to congenital urethral valve; dehydration; dilation of pancreas acini; and emaciation.

## COMMENT

The diagnosis of cystinosis was established in this patient on the basis of the characteristic morphologic findings and by the chemical isolation of large amounts of cystine from the mesenteric lymph nodes, spleen, and liver. This amino acid was also found to a lesser extent in the mesenteric adipose tissue. Many cells indicative of cystine deposits were seen in the bone marrow. The renal lesions conformed to those observed by others.[11] The morphologic findings in this patient consisted of crystalline-cystine deposits chiefly throughout the reticuloendothelial system and are similar to those recorded in the literature. Cystine deposits were noted in the stroma of almost every organ except the nervous and muscular tissue.[4] Marked renal damage with fibrosis of the interstitial tissue and sometimes glomerular sclerosis [12] has been described, but in two patients significant renal lesions were not found.[13]

11. Lignac.[5] Waser, P.: Pathologische Anatomie der Cystinspeicherungskrankheit anhand eines im Frühstadium verstorbenen Kindes, Helvet. paediat. acta **1**:206, 1946. Beumer, H., and Weppler, W.: Über die Cystinkrankheit der Ersten Lebenszeit, Klin. Wchnschr. **16**:8, 1937. Rössle, R.: Beiträge zur Frage der Speicherungskrankheiten, Verhandl. deutsch. path. Gesellsch. **31**:133, 1938.

12. (*a*) Russell and Barrie.[10] (*b*) Roulet, F.: Das anatomische Bild der Cystinkrankheit mit Zwergwuchs, Ann. paediat. **156**:284, 1941. (*c*) Looser, R.: Ein Fall von Cystinspeicherung mit renalem Zwergwuchs und Rachitis, ibid. **163**:251, 1944.

13. (*a*) Hottinger, A.: Zur Cystindiathese, Ann. paediat. **169**:272, 1947. (*b*) Benoit, W.: Calcinosis universalis, Beitr. path. Anat. u. allg. Path. **94**:611, 1935.

Cystinuria is not a constant finding in cystinosis. Cystine has been demonstrated in the urine in only five patients,[14] and in one other a cystine stone was found in the renal pelvis at autopsy.[15] In two cases even chemical tests failed to demonstrate this amino acid in the urine.[16] Cystinuria may be present early in the course of the disease and disappear later when renal damage supervenes. In one patient several amino acids other than cystine were found in the urine by paper chromatography.[6b] Glycosuria with normal blood sugar and hypophosphatemia are other less constant findings.

Once suspected, the diagnosis of cystinosis can be established readily by the demonstration of the typical crystals in the smear of the aspirated bone marrow.[17] This procedure should be most helpful, since diffuse bone-marrow involvement has been noted in almost every patient at autopsy. It has been suggested that a biopsy of a lymph node be taken.[4] Cystine deposits have also been seen in the cornea on slip-lamp examination.[18]

The differential diagnosis includes "resistant rickets" (osteomalacia), diabetes insipidus, glycosuria, and unexplained fevers, as well as the Fanconi syndrome. The latter disorder is characterized by osteomalacia, hypophosphatemia, renal glycosuria, normal blood concentration of urea and amino acids, and aminoaciduria without cystinuria.[19] The differentiation of the Fanconi syndrome and cystinosis may be made in some instances only by the demonstration of cystine crystals in the tissues. In fact Fanconi,[6a] as well as Rapaport [3] and Dent,[19] considers cystinosis a variant of the Fanconi syndrome.

Cystinosis can be treated only by general supportive measures. Choline has been shown to decrease the urinary excretion of cystine and has been suggested as a therapeutic agent.[20] It is considered a familial disease, inherited as a recessive Mendelian trait,[4] but a familial incidence has been demonstrated in only seven cases.[21] After the diagnosis was established in our patient, his family was investigated without finding evidence of cystinuria, renal calculi, nephritis, dwarfism, or rickets. Single urine samples from three siblings, both parents, three grandparents, and three paternal and three maternal aunts and uncles failed to show cystine by the nitroprusside method of Brand [22] upon repeated examinations three months apart.

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14. (*a*) Pache, H. D.: Über die Cystein-Cystinstoffwechselstörung der ersten Lebenzeit und ihre Beziehung zu Zwergwuchs und renaler Rachitis, Ztschr. Kinderh. **62**:1, 1940. (*b*) Van Creveld, S., and Grunbaum, A.: Renal Rickets and Cystinuria, Acta paediat. **29**:183, 1942. (*c*) Looser.[12c] (*d*) Fanconi.[6a]

15. Lignac, G. O. E.: Zystinbefunde bei einer bestimmten Kinderkrankheit, Verhandl. deutsch. path. Gesellsch. **21**:303, 1926.

16. Fanconi and Bickel.[6b] Hottinger.[7]

17. Esser, M.: Zur Diagnose der Cystinkrankheit, Ann. paediat. **156**:344, 1941.

18. Bürki, E.: Über Augenveränderungen bei der Cystinkrankheit, Ann. paediat. **156**:324, 1941.

19. Dent, C. E.: Partition Chromatography on Paper: A Qualitative Method for Identifying Amino Acids in Urine, and Its Application to the Fanconi Syndrome, Conference on the Metabolic Aspects of Convalescence, Transactions of the Fourteenth Meeting, Nov. 12-13, 1946, New York, Josiah Macy Jr. Foundation, 1947, pp. 126-157.

20. Hottinger.[13a] Van Creveld and Grunbaum.[14b]

21. Russell and Barrie.[10] Pache.[14a] Hottinger.[7] Van Creveld and Grunbaum.[14b] Looser.[12c] Fanconi and Bickel.[6b]

22. Lewis, H. B.: The Occurrence of Cystinuria in Healthy Young Men and Women, Ann. Int. Med. **6**:183, 1932.

Cystinosis is generally regarded as a congenital metabolic defect.[3] A direct relation between cystinuria of the adult and cystinosis of children has not been established. Fanconi [6a] and others postulate that the excess excretion of cystine produces renal damage with retention of the amino acid and saturation of the blood followed by crystallization and deposition in the reticuloendothelial system. This concept is difficult to reconcile with the observation of little or no demonstrable renal damage at autopsy in some cases. Freudenberg [4] suggests that the deposits of cystine crystals occur at the sites of excess formation, since cystine has been found in the avascular cornea but never in the blood vessels. Further deposition of cystine occurs when renal damage becomes established.

In retrospect, our patient presented a typical clinical picture of cystinosis. The onset of this disorder is often sudden and usually occurs in a previously normal infant at the age of 6 to 12 mo. Male infants are more commonly afflicted than females. Anorexia, refusal of solid foods with a craving for liquids, polyuria, dehydration, constipation, and unexplained fever are the outstanding symptoms. Rapid loss of weight occurs at the beginning of the illness, but later the weight remains constant. Growth in height is decreased but not arrested. Periods of exacerbation occur about once a month. The disease generally progresses slowly for several years, and the child may become dwarfed. "Rickets resistant to treatment" is described in 11 cases. Physical examination generally reveals only inanition and dehydration. Enlargement of the spleen and liver was noted in a few cases. Death occurs in uremia or subsequent to intercurrent infection, to which the patients are highly susceptible. Most patients die in early childhood, although one survived until the age of 16.[10]

Cystinosis has been studied extensively in Europe. Only two cases have been described in the American literature, but increasing familiarity with this disorder may well uncover others. The clinical and particularly the morphologic manifestations are typical, and the diagnosis once considered can be readily established without complicated laboratory procedures. At present therapy consists of only supportive measures. Cystinosis, however, affords a unique opportunity for the study of basic protein metabolism and its disorders.

## SUMMARY

Cystinosis, a rare inborn error of protein metabolism, was found at autopsy in a 3-yr.-old boy. Cystine was isolated chemically in large amounts from various organs.

The clinical and morphologic manifestations of this disorder are reviewed.

# SITUS INVERSUS WITH LEVOCARDIA

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SITUS inversus of the abdominal viscera with the heart occupying its normal position seems to occur rather infrequently according to Taussig's book on congenital malformations of the heart.[1] Three cases are mentioned by Taussig, with a report of one autopsy. Eek [2] reports one case in which the vena cava superior was left of the vessel trunk, the hilar vessels pulsated heavily, and the apex cordis was directed forward and medially. Hoekstra [3] published a case report of a child, aged 8 mo., in whom he found a three-lobed left lung and a two-lobed right lung, the heart in its normal position but the left ventricle forming the left lateral border of the heart. The interventricular septum presented a defect, and the pulmonary artery was hypoplastic. In order to have an idea of the origin of this congenital defect, Hoekstra imagined that the heart in situs inversus totalis made a rotation from the right side of the thorax backward to the left. This torsion went too far and caused strangulation of the pulmonary artery. We have been happy to find a new case in which partial autopsy revealed a real complex of malformations.

## REPORT OF A CASE

Mr. and Mrs. R., healthy and recently married people, expected their first child. In the first and second months of pregnancy, serious tonsillitis with septicemia nearly caused the death of Mrs. R., but afterward her condition was splendid and parturition was without difficulties. Baby J. R., a stout boy weighing 3,260 gm., breathed immediately after birth, but his skin remained slate-colored, with brownish-pigmented mucosae. The whole aspect of the baby had some resemblance to that of a Negro baby. The respirations were laborious and rapid; the pulse was strong, full, and a little too slow. When the first trial was made to feed the baby, he turned black and seemed exhausted, although he seemed hungry and did not cough or vomit after feeding.

At this time I saw the baby for the first time; the skin had a black-blue-brownish color. The finger tips and toe tips were normal. On percussion the heart was found to be enlarged to the left side, without abnormal sounds on auscultation. In the abdomen the left side of the hypochondrium seemed filled with a "tumor" with an edge like the liver. The roentgenogram gave the clue; the liver shadow was found at the left, and the heart was apparently in the normal position. The lungs exhibited a rather heavy emphysema. The Wassermann reaction was negative; neither rhesus nor A-B-O antibodies could be found. Blood examination revealed a hemoglobin concentration of 25 gm. per 100 cc., with 4,800,000 erythrocytes and 15,600 leucocytes; a differential count showed 2% eosinophils, 1% basophils, 5.5% stab forms, 51% polymorphonuclear leucocytes, 36.5% lymphocytes, and 4% monocytes. On counting, 200 leucocytes, nine normoblasts, and four primary erythroblasts were found. The urine contained a trace of albumin.

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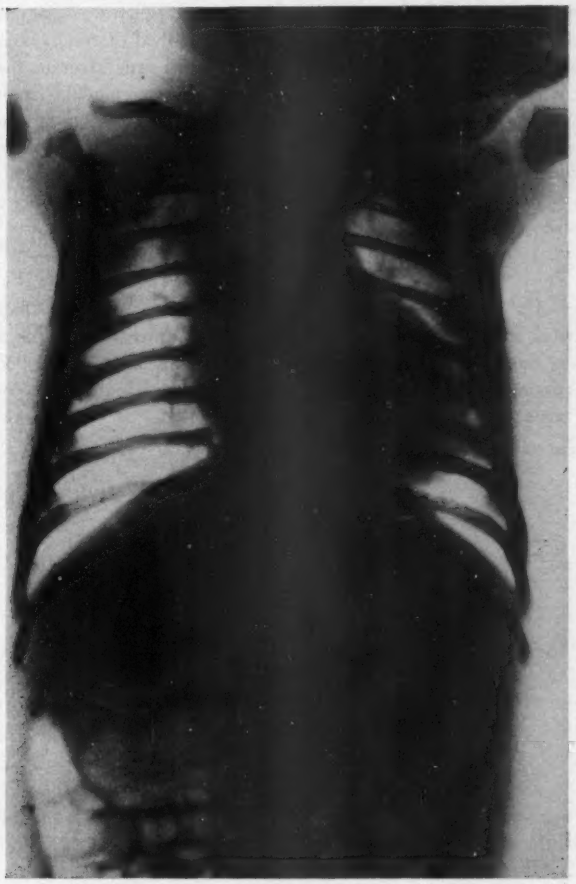
1. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947, p. 513.

2. Eek, S., and others: Morbus Caeruleus: An Analysis of 114 Cases of Congenital Heart Disease, edited by E. Mannheimer, Basel, S. Karger, 1949, p. 112.

3. Hoekstra, R. A.: Normal, Abnormal and Pathologic Development of Cardiovascular System: Etiopathogenetic and Clinical Study, Geneesk. bl. klin. en lab. prakt. **43**:29, 1949.

Even with the most careful feeding the child rapidly declined and died suddenly on the fifth day. Permission for partial autopsy was obtained. In the abdomen the liver was found on the left side and the spleen on the right. The cecum and ascending colon were on the left side and the descending colon and the sigmoid on the right. The pylorus was on the left. In the thorax a three-lobed lung was found on the left and a two-lobed lung on the right. When the trachea was opened, the main bronchus on the right side was found to form a more acute edge with the



Roentgenogram of situs inversus with levocardia, cor trilocularis biatriatum, and extra vena cava superior with abnormal course of the pulmonary veins.

trachea than did the main bronchus on the left side. The aortic arch passed over the right main bronchus and had a position right of the esophagus, which was bent to the left and had a rather normal course. The thymus was as large as commonly found in babies of this age. The heart was very large, and the apex was directed to the left. The pericardium was normal and contained no fluid. On opening the heart only one ventricle was found; its right side seemed to be functionally the wall of the right ventricle. The aorta was situated before and to the right side of the hypoplastic pulmonary artery and had its origin from the middle of

the ventricle. Three normal cusps and a normal origin of the coronary arteries were found. The aorta, in dextroposition, had a normal arch without a ductus arteriosus persistens. The pulmonary artery permitted only a very fine needle to enter its lumen and showed remains of cusps. The vena cava entered into the right atrium; the pulmonary veins together with another vena cava superior entered into the left atrium.

## COMMENT

The necropsy findings in this case of situs inversus, which was diagnosed during life by examination and roentgenogram, have a great deal of resemblance to those in Hoekstra's case. We must imagine that the heart in situs inversus turned backward to the left so far that the pulmonary artery was strangulated. In our case the sole ventricle and the abnormal course of the pulmonary veins coming into an extra vena cava superior complicated the difficulties in oxygenation. It is unfortunate that a thorough examination of the arteries and veins could not be done. An explanation of the abnormal development cannot be given. The influence of the very serious disease of the mother can only be guessed.

## SUMMARY

The case of a 5-day-old white male infant who was born as a "blue baby" is reported. Situs inversus partialis and congenital malformation of the heart were the diagnoses during life. Necropsy revealed situs inversus with levocardia, cor triloculare biatriatum, and an extra vena cava superior, with abnormal course of the pulmonary veins.

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# SELECTIVE PANCREATIC DEFICIENCY

## Absent Amylase, Diminished Trypsin, and Normal Lipase

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THE PURPOSE of this report is to point out the existence of persons who have a persistent deficiency in one or another of the three digestive enzymes of the pancreas, while retaining normal secretion of the others, associated with corresponding symptoms. It is further desired to distinguish this disorder from the similar but well established disease fibrosis of the pancreas, in which all three enzymes are found to be absent regularly. It is hoped this report will stimulate others to note and report on similar experiences so that the frequency and nature of this disorder may be determined. Reports of the histology of the pancreas in such patients would be particularly helpful, as we have not had an opportunity to see the pancreas in our patients.

TABLE 1.—*Gelatin Liquefaction Test for Trypsin*

| | Dilution of Pancreatic Juice * | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1:20 | 1:25 | 1:50 | 1:100 | 1:200 | 1:400 | 1:800 | 1:1,600 |
| Normal duodenal juice | L | L | L | L | L | L | L | L |
| Fibrosis of the pancreas | L | S | S | S | S | S | S | S |
| Patient without secretin | S | S | S | S | S | S | S | S |
| Patient after secretin | L | L | SS | S | S | S | S | S |

Amylase: 0

Lipase: 3.9 ml. 0.01 N NaOH/ml. of duodenal fluid (normal = more than 1 ml. 0.01 N NaOH)

* L indicates liquefaction; S, solid; SS, semisolid.

In the course of examining the duodenal contents for pancreatic enzymes in infants and children with chronically abnormal stools we have encountered two instances in which one or two enzymes could not be detected. This was apparently a congenital and permanent defect. The first child showed absence of trypsin but normal amounts of lipase and amylase. This finding was confirmed upon numerous occasions, and the aberration was apparently an irreversible abnormality of pancreatic function. Furthermore, this child had none of the respiratory phenomena usually associated with fibrosis of the pancreas. Unfortunately, he died at home at about 4 yr. of age, and no necropsy was performed. In their review of pancreatic function in children, Farber, Shwachman, and Maddock [1] refer to this patient.

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1. Farber, S.; Shwachman, H., and Maddock, C. L.: Pancreatic Function and Disease in Early Life: I. Pancreatic Enzyme Activity and The Celiac Syndrome, J. Clin. Invest. **22**:827-838, 1943.

The second child, upon whom the studies described below were performed, had a disorder in many ways similar to that of the first. His duodenal fluid had normal lipase activity, markedly diminished tryptic activity, but no amylase activity.[2] These findings were present in numerous samples of duodenal fluid (Table 1).

### REPORT OF A CASE

D. T., a 13-yr.-old white boy, was admitted to the University Hospitals because of malnutrition and underdevelopment. The family history failed to reveal any evidence of intestinal abnormalities, and the only sibling, a 16-yr.-old boy, was without complaints. The child was the result of a normal, full-term pregnancy, and there was no history of neonatal distress. At 8 mo. of age he weighed 6.3 kg., but even before this he had had several changes in formula because of large, foul, bulky stools. It was the impression of his attending physician that he suffered from some kind of intestinal insufficiency. A "celiac type" of diet, consisting of bananas, curds, fat-free milk, scraped beef, and cottage cheese, was started. On this regimen he began to gain weight at a more rapid rate, and when he was 4 mo. of age weighed 7.6 kg.

From 2 to 13 yr. of age the patient was treated by his family physician for a number of minor complaints. These included a urethral stricture, which was relieved by meatotomy, and at the age of 6 yr. an attack which appeared to be asthmatic bronchitis. When 10 yr. old the patient had a gangrenous appendix removed. Four months before admission to the University Hospitals the child was seen by his doctor for abdominal pain. The continuing presence of abnormal stools was noted.

When admitted to the University Hospitals, the boy reported that carbohydrates and fat caused distention and a feeling of abdominal discomfort. At that time he was having up to six large foul-smelling, light-colored, bowel movements a day. He was a thin, cooperative, poorly nourished, underdeveloped 13-yr.-old boy who appeared neither acutely nor chronically ill. The rectal temperature was 98.6 F., pulse rate 70; respirations were 16 per minute, and blood pressure was 106/70 mm. of mercury. The weight was 31 kg. The abdomen was noted to be slightly distended, and there was moderate tenderness over both lower quadrants. The liver was 3 cm. below the right costal margin. No other abnormalities were noted.

The hemoglobin was 13 gm. per 100 cc., and the white blood cell count was 5,200; the differential count was 41% polymorphonuclear leucocytes, 63% lymphocytes, and 6% monocytes. The mean corpuscular hemoglobin was 30$\mu\gamma$. The mean corpuscular diameter was 7.3 $\mu$. The mean corpuscular volume was 80 cu. $\mu$, while the mean corpuscular hemoglobin concentration was 37%. Serum protein was 7.1 gm. per 100 ml. with 5 gm. of albumin and 2.1 gm. of globulin. The blood calcium was 10.2 mg. per 100 ml. and the phosphorus 4.1 per 100 ml. The serum alkaline phosphatase was 26 King-Armstrong units per 100 ml. Urine examination revealed a specific gravity of 1.021 with a pH of 6; no abnormal constituents were demonstrated. A tuberculin test (0.1 mg. of old tuberculin) elicited a negative reaction, as did a Schick test. An oral glucose tolerance test showed a fasting level of 75 mg. per 100 ml. of blood with a peak at one and a half hours of 132 mg. per 100 ml. An examination of the duodenal fluid for the determination of pancreatic ferments revealed the following facts upon three occasions: no amylase was present, and lipase activity was within normal range, 3.9 to 9.5 units per ml. Tryptic activity was considerably reduced, but on each occasion it was possible to demonstrate a definite residual amount of activity; salivary amylase was present. X-ray examination of the chest failed to reveal any evidence of infection. X-ray examination of the small bowel after a barium sulfate meal showed an unusual granular appearance of the mucosal surfaces. The large bowel was not abnormal. A vitamin A absorption test revealed a fasting level of vitamin A of 35 $\gamma$ per 100 ml. with a peak at 7 hr. of 540 $\gamma$ per 100 ml. The carotene level was 120 $\gamma$ per 100 ml.

It was not possible to make a diagnosis of fibrosis of the pancreas with the data available. The evidence against this diagnosis was (1) absence of pulmonary infection shown by x-ray and history; (2) a normal vitamin A absorption test (it has not been our experience in the past that

2. The methods used in the present study have been described in a previous report from this clinic (Lowe, C. U., and May, C. D.: Metabolic Studies in Patients with Intolerance to Complex Carbohydrate, Am. J. Dis. Child. **81**:81-98 (Jan.) 1951.

children with fibrosis of the pancreas have a normal vitamin A absorption test [3]) and (3) the presence of normal lipase activity in the duodenal fluid. In keeping with this was an absorption of fat much higher than we have ever encountered in patients with fibrosis of the pancreas. The high absorption was demonstrated while the patient received almost 60 gm. of fat per day. In favor of the diagnosis of a primary deficiency of tryptic activity was the relatively large output of nitrogen in the stools on a protein intake of 60 gm. a day.

Although little is known of the factors necessary to make inactive trypsin active, it was thought that possibly this patient lacked them. Our efforts to activate his duodenal fluid were unsuccessful.

It was our impression, therefore, that this patient suffered from a primary deficiency of trypsin and absence of amylase.

### SPECIAL TESTS

Fat and nitrogen absorption studies were performed in order to obtain corroborative information concerning the absence of amylase, decrease in trypsin, and presence of lipase. No direct measurement of carbohydrate absorption is available, but it seems important to point out that this patient had a normal oral glucose tolerance curve, a finding that has also been observed in patients with complete pancreatic achylia [8] but not in those with other types of definite intestinal insufficiency.[4] Results of fat and nitrogen absorption can be appreciated from examination of Table 2.

TABLE 2.—*Fat and Nitrogen Absorption Data*

| | Fat Absorbed, % | Stool Nitrogen Gm./Day | Nitrogen Absorbed, % |
|---|---|---|---|
| Normal for 12 yr. old persons * | 95 | 1.43 | 90 |
| Fibrosis of the pancreas | 60 * | 4.40 † | 45 † |
| Patient D. T. | 85.3 | 1.87 | 80 |

* An average figure for all ages taken from Shohl. (Shohl, A. T.: Further Studies of Nitrogen and Fat Metabolism in Infants and Children with Fibrosis of the Pancreas, J. Pediat. **32**: 180-183, 1948.)

† These figures were taken from balance studies performed on a patient 11 yr. of age. (Shohl, A. T.; May, C. D., and Shwachman, H.: Studies of Nitrogen and Fat Metabolism on Infants and Children with Pancreatic Fibrosis, J. Pediat. **23**: 267-279, 1943.) They seem to be figures suitable for comparison with patient D. T.

Although minimal malabsorption of fat seems to be present, the degree of absorption is much higher than we have ever observed in a patient with fibrosis of the pancreas. The azorrhea is of an amount one might expect with moderately diminished tryptic activity.

Since it was unlikely that a pathologic process as complete and irreversible as that seen in fibrosis of the pancreas could allow the elaboration of lipase but not the other pancreatic enzymes, it seemed wise to look for other ways to explain this patient's peculiarities. It has long been known that trypsin as elaborated by the pancreas is not proteolytic.[5] A source of "activators" free of trypsin was sought. It seemed possible that some substance which normally activated trypsin might be present in either the succus entericus or the gastric juice of a patient with fibrosis of the pancreas, although trypsin would be absent. Accordingly, material was obtained from such a patient, and experiments devised to "activate" the trypsin

3. Lowe, C. U.; May, C. D., and Reed, S. C.: Fibrosis of the Pancreas in Infants and Children: A Statistical Study of Clinical and Hereditary Features, Am. J. Dis. Child. **78**:349-374 (Sept.) 1949.

4. MacLean, A. B., and Sullivan, R. C.: Carbohydrate Intolerance in Infants and Young Children with Celiac Disease, Am. J. Dis. Child. **38**:16-25 (July) 1929. Svensgaard, E.: Blood Sugar in Intestinal Infantilism, Acta paediat. **9**:22-29, 1929.

5. Kühne, W.: Über die Verdauung der Eiweissstoffe durch den Pankreassaft, Arch. path. Anat. **39**:130-174, 1867.

of our patient were performed as outlined in Table 3. In a further attempt to obtain active pancreatic digestive enzymes, duodenal fluid was aspirated after the patient had received a dose of secretin.[6]

Inspection of the data in Table 4 resulting from these experiments will reveal that neither the intestinal secretions used nor other so-called "activators" were capable of causing the patient's duodenal fluid to exhibit normal tryptic activity.

## COMMENT

We have been able to find few reports of patients with persistent selective deficiency in one or two pancreatic enzymes.[7] It has not been possible to find any balance data on such patients calculated to corroborate these deficiencies. Veghelye [7b] reported analyses of enzymes in 47 normal children and found there was "parallelism" between the outputs of each of the ferments. He also examined the pancreatic enzymes in 32 children with scarlet fever and found depression of each enzyme during the second week of illness.[7c] Four patients showed severer depres-

TABLE 3.—*Protocol for Attempts at "Activation" of Patient's Duodenal Juice, Milliliters of Material Used*

| Tube No. | Fibrosis of the Pancreas: Duodenal Juice | Fibrosis of the Pancreas: Gastric Juice | Calcium* | Secretin† | Ventriculin‡ | $NaHCO_3$§ | Patient's Duodenal Juice‖ |
|---|---|---|---|---|---|---|---|
| 1 | 1 | .. | .. | .. | .. | 1 | #1‖ 1 ml. |
| 2 | 1 | .. | .. | .. | .. | 1 | #2‖ 1 ml. |
| 3 | .. | .. | 1 | .. | .. | 1 | #1 1 ml. |
| 4 | .. | .. | .. | .5 | .. | 1.5 | #1 1 ml. |
| 5 | .. | .. | .. | .. | 1 | 1 | #1 1 ml. |
| 6 | .. | 1 | .. | .. | .. | 1 | #1 1 ml. |
| 7 | .. | 1 | .. | .. | .. | 1 | #2 1 ml. |
| 8 | .. | .. | .. | .. | .. | 1 | #1 1 ml. |
| 9 | .. | .. | .. | .. | .. | 1 | #2 1 ml. |

* Calcium gluconate, 1% solution.
† Secretin, 15 mg./cc.
‡ Ventriculin, 20% solution.
§ $NaHCO_3$, 5% solution.
‖ Sample 1 before secretin, sample 2 after secretin.
After mixing, tubes were incubated for 30 min. at 37 C.

sion than the others. At autopsy, it was possible to demonstrate necrosis of the pancreas in the one patient in this group who died. Two children had an elevation of serum amylase and lipase, indicating obstruction of the pancreatic ducts, but in no patient did a permanent lack of one or more enzymes with persistence at normal levels of excretion of the others develop.

McDougall [7d] reported extensive studies on the pancreatic enzymes of 165 children. Two children were found with absence of trypsin and absent or variable amounts of amylase and lipase. Neither had a history compatible with typical fibrosis of the pancreas, and in one instance an anomaly of the pancreatic duct was

6. Secretin was supplied by Eli Lilly & Company through the courtesy of Dr. Edward Campbell.

7. Veghelye, P. V.: (*a*) Secondary Pancreatitis, Am. J. Dis. Child. **74**:45-51 (July) 1947; (*b*) Pancreatic Enzymes: Normal Output and Comparison of Different Methods of Assay, Pediatrics **3**:749-763, 1949; (*c*) Pancreatic Function in Scarlet Fever, ibid. **4**:94-101, 1949; correction **4**:824, 1949. (*d*) McDougall, C.: Clinical Evaluation of Abnormal Enzyme Content on the Pancreatic Juice of Children, Pediatrics **5**:114-126, 1950.

suggested. A second group, of five children, had temporary depression of trypsin and, occasionally, the two other enzymes during periods of ill health. The condition of three of these returned to normal; a fourth died, and the fifth returned to almost normal. The author calls attention to a similar phenomenon reported by Veghelye. A third group of the children had depression of lipase alone. This was measured during an acute illness. All except one was shown subsequently to have normal lipase. Pertinent to the present case report, no persons were found with a reduction of tryptic activity and absence of amylase.

Farber has suggested that the disease of infants and children called fibrosis of the pancreas need not always produce complete achylia pancreatica.[8] He proposed that the disease may develop slowly, with more or less loss of exocrine function of the pancreas. Christensen and Shwachman [9] have been sympathetic with this thought, basing their reasoning upon amino acid absorption tests performed on patients with fibrosis of the pancreas. More recently, Gibbs, Bostick, and Smith [10] have reported

TABLE 4.—*Gelatin Liquefaction Test of "Activated" Duodenal Juice*

| Tube No.* | Gelatin | 5% $NaHCO_3$ | 1:3 | 1:6 | 1:12 | 1:24 | 1:48 |
|---|---|---|---|---|---|---|---|
| 1 | 2 cc. | 0.5 cc. | L | L | SS | S | S |
| 2 | 2 cc. | 0.5 cc. | L | L | L | L | SS |
| 3 | 2 cc. | 0.5 cc. | L | SS | S | S | S |
| 4 | 2 cc. | 0.5 cc. | SS | S | S | S | S |
| 5 | 2 cc. | 0.5 cc. | SS | S | S | S | SS |
| 6 | 2 cc. | 0.5 cc. | L | SS | S | S | S |
| 7 | 2 cc. | 0.5 cc. | L | L | L | SS | S |
| 8 | 2 cc. | 0.5 cc. | L | SS | S | S | S |
| 9 | 2 cc. | 0.5 cc. | L | L | L | L | SS |
| 10† | 2 cc. | 0.5 cc. | S | S | S | S | S |
| 11‡ | 2 cc. | 0.5 cc. | S | S | S | S | S |
| 12§ | 2 cc. | 0.5 cc. | S | S | S | S | S |
| 13‖ | 2 cc. | 0.5 cc. | SS | SS | SS | S | S |

* Numbers 1 to 9 refer to the same tube numbers as used in table 3. Dilutions are indicated.
† Secretin 1 ml., 15 mg./cc.
‡ Calcium 1 ml., 1%.
§ Ventriculin 1 ml., 20%.
‖ Pancreatin 1 ml.
S indicates solid (no activity); SS, semisolid (minimal activity), and L, liquid (normal activity).

clinical and necropsy observations which may be interpreted as in keeping with Farber's original suggestion.

A considerable collection of data favors the concept that the disease fibrosis of the pancreas is fully developed when clinically evident. The remarkable agreement between the expected attack rate in families of a disease inherited as a Mendelian recessive characteristic and that found in families in which fibrosis of the pancreas occurred would seem to make the appearance of any incompletely expressed cases unlikely.[3] It would thus seem that the phenomena described above may deserve to be classed apart from fibrosis of the pancreas. Also, no pulmonary lesion was present in our two cases.

8. Farber, S. S.: Medical Progress: Pancreatic Insufficiency and the Celiac Syndrome, New England J. Med. **229**:653-657 (Oct. 21); 682-687 (Oct. 28) 1943.

9. Christensen, H. N., and Shwachman, H.: Determination of the Plasma Glycine After Gelatin Feeding as a Diagnostic Procedure for Fibrosis of the Pancreas, J. Clin. Invest. **28**:319-321, 1949.

10. Gibbs, G. E.; Bostick, W. L., and Smith, P. M.: Incomplete Pancreatic Deficiency in Cystic Fibrosis of the Pancreas, J. Pediat. **37**:320-325, 1950.

SUMMARY

The case of a patient with absent amylase, decreased trypsin and normal lipase in material aspirated from his duodenum, together with a special laboratory test, is reported.

The following facts are stressed: With the decrease in tryspin there was a decrease in nitrogen absorption as shown by balance studies. To confirm the normal lipase, it was demonstrated that the vitamin A absorption was normal and the fat absorption was almost within normal limits by balance study.

It is hoped that this rather limited report will stimulate other observers to report upon similar patients so that it may in time be possible on clinical as well as on pathological and laboratory grounds to separate them from patients with other types of intestinal insufficiency.

# Progress in Pediatrics

## BORIC-ACID POISONING

### Report of a Case and Review of the Literature

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BORIC acid and sodium borate are sufficiently poisonous to cause severe symptoms and death when used in amounts commonly considered to be perfectly harmless. Boric acid is readily absorbed by a number of different routes and is particularly insidious in that symptoms may be minimal until a lethal or near lethal dose has been absorbed. A number of cases of boric-acid poisoning have been reported in the literature, but relatively few are accompanied with laboratory data, autopsy findings, or tissue analyses for boron. A number of deaths, particularly in infants, are mentioned in the literature but have not been adequately reported. References to boric-acid poisoning are almost completely absent from the pediatric journals. The following case is presented because it occurred in an older infant without a severe complicating disease and because a complete autopsy, including tissue analysis for boron, was performed.

#### REPORT OF A CASE

I. C., a 9-mo.-old white girl weighing 9,150 gm. (20 lb. 2 oz.), was admitted to Strong Memorial Hospital at 2:00 a. m. on Feb. 16, 1950, in a semicomatose state. Her present illness had begun 10 days previously with the development of a diaper rash (ammoniacal dermatitis) and mild anorexia. The diaper rash was treated with home remedies without success, and because the dermatitis was progressing, the family pediatrician was consulted on Feb. 9. The father was instructed to apply zinc oxide (Lassar's plain zinc) paste to the diaper area. In addition, without the physician's knowledge, the father sprinkled powdered boric acid freely on the diaper and skin lesions. The infant's condition remained unchanged; her appetite continued poor, and on Feb. 13 she vomited three times. The following day she was placed on a weak tea and skimmed-milk formula, and on Feb. 15 she was given just weak tea, but her fluid intake remained inadequate, and she continued to vomit two or three times a day.

On Feb. 15, her buttocks became excoriated and extremely erythematous, her temperature was elevated for the first time, and she became very lethargic. That evening her respirations became rapid and shallow, and she became semicomatose, with a high fever. Shortly before admission a bright red confluent macular eruption of her face, head, neck, and extremities developed; she vomited coffee-ground material and passed one bloody stool.

Past medical history was noncontributory. The infant had been in excellent health and had had no diseases.

Physical examination revealed a well-developed, well-nourished, semicomatose, dehydrated, moderately cyanotic, and extremely ill 9-mo.-old white girl. The temperature was 40.5 C. (104.9 F); respiration rate, 60 a minute, pulse rate, 180 a minute. There was an extremely erythematous, confluent macular eruption of the skin of the head, face, neck, and upper extremities. The buttocks, perineum, and lower abdomen were covered with a thick paste (zinc oxide

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paste) and sprinkled liberally with boric acid powder. Gentle washing revealed marked excoriation of the buttocks, vulva, and perineum, with oozing of bright red blood. The vulva and perineum were edematous. The skin of the auricles was bright red, the nail beds of the fingers were bright pink, and those of the toes were dusky and cyanotic. The anterior fontanel was depressed. Pupils were equal in size and reacted to light. The eyes showed continuous wandering nystagmoid movements. The ocular pressure was decreased, and the conjunctivas were markedly injected. The lips were dry and excoriated. The mucous membranes of the mouth and pharynx were extremely red, and the pharynx was filled with brown vomitus. The neck was supple. The respiratory rate was rapid but regular; excursions were shallow but equal bilaterally. Coarse rhonchi were heard throughout the chest. It was thought that these were transmitted from the pharynx. There was tachycardia (180 a minute). The heart sounds were muffled and of poor quality. No murmurs were heard. The abdomen was soft and sunken. The liver was palpable 2 cm. below the costal margin. The spleen was not palpable. No bowel sounds were heard. The patient varied from a semicomatose to a comatose state, intermittently responding to painful stimuli. Neurological examination was otherwise normal. The tendon reflexes were equal and normal.

*Laboratory Data.*—Laboratory examination revealed the following: red blood cells, 6,700,000; hemoglobin, 12.6 gm. per 100 cc.; white blood cells, 14,800, and a differential cell count of 69% neutrophiles; 28% lymphocytes, 1% monocytes, 2% eosinophiles, and no basophiles. The red cells appeared normocytic and normochromic. There appeared to be a normal number of thrombocytes on the smear. A specimen of urine obtained by catheter was clear and yellow; the reaction was acid; it contained albumin (1+) and no sugar, and there was a trace of acetone. On microscopic examination an occasional red blood cell was found per each high power field in a centrifuged specimen. The blood nonprotein nitrogen was 75 mg. per 100 cc.; the serum chlorides were 103 mEq. per liter (602 mg. per 100 cc. NaCl), and the carbon dioxide-combining power was 23.6 mEq. per liter (52 vol. %). A urine specimen obtained by catheter contained 1.6 mg. of boron per milliliter (9.12 mg. boric acid per milliliter). Blood cultures showed no growth, and nose and throat cultures showed no pathogens. Escherichia coli and Pseudomonas aeruginosa were isolated from the skin of the perineum. Aerobacter aerogenes was cultured from the urine.

*Hospital Course.*—The infant was given oxygen immediately, and after the drawing of blood for the determination of blood chemistry and for culture, a cut-down was performed on the right saphenous vein and a continuous intravenous drip maintained. She was given blood (100 cc.), dextrose and saline solution, aqueous penicillin (100,000 units), and adrenal cortical extract (2 cc.) intravenously. She was then given dihydrostreptomycin, 0.050 gm. intramuscularly every three hours; aqueous penicillin, 50,000 units intramuscularly every three hours, and a vitamin K preparation parenterally. Three hours after admission her temperature rose to 41 C. (105.8 F.), and the patient began having generalized twitching, for which she was given phenobarbital sodium subcutaneously, tepid water sponges, and acetylsalicylic acid. Shortly thereafter it was noticed that the degree of erythema of the face, neck, and extremities had increased. Approximately four hours after admission her temperature began to fall, but her general condition remained unchanged. She continued comatose and had intermittent convulsions; her temperature reached a low of 36.5 C. (97.9 F.), and she died quietly 26 hr. after admission.

*Postmortem Findings.*—At autopsy, performed seven hours after death, the following pathological diagnoses were made: (1) ulceration of the skin of the perineum, (2) acute hemorrhagic enteritis, (3) minimal ascites, (4) cloudy swelling and central necrosis of the liver, and (5) pulmonary congestion and edema.

In addition there was evidence of the following: (1) mild cloudy swelling of the myocardium, (2) congestion of the pyramids and possible but questionable cloudy swelling of the convoluted tubule cells of the kidney, (3) mild acute splenic reaction, (4) marked edema of the wall of the gall bladder, and (5) marked involution of the thymus with numerous degenerating Hassalls' corpuscles. The adrenals, pancreas, and bone marrow were normal. The brain weighed 1,030 gm., the normal weight being about 750 gm. No gross abnormalities were seen, and no specific changes were found on microscopic examination.

Determination of the boron content of the urine and tissues was done by Luville T. Steadman, Ph.D., Chief of Section (Spectroscopy), Division of Biophysics, Atomic Energy Project at the University of Rochester.

Boron was determined by spectrographic analysis employing the D. C. carbon arc. The urine was suitably diluted, and a 0.1-ml. sample was pipetted into the carbon electrode and dried therein. The tissues were wet ashed with nitric acid and a 0.1-ml. sample of the digest was similarly analyzed. The boron was measured by the intensity of the spectrum line 2,497.7 A. and read from a calibration curve previously established using known amounts of boron and platinum as the internal standard.

*Diagnosis and Therapy.*—The diagnosis of boric-acid poisoning was suggested from the clinical appearance of the infant on admission, and the parents were asked what they had been applying to the diaper rash. About 9 oz. (250 gm.) of powdered boric acid had been used in the preceding several days. It had been sprinkled liberally on the diapers and directly onto the skin.

Therapy was symptomatic, since there is no known specific treatment for boric-acid poisoning. Fluids and blood were given intravenously to combat the circulatory collapse and dehydration. Adrenal cortical extract was used because of the collapse and generally poor appearance of the infant. Unfortunately, studies of the clotting mechanism were not done, but vitamin K was used in view of the possible liver damage and the obvious gastrointestinal bleeding. Penicillin and dihydrostreptomycin were given because we could not be sure that we were not also dealing with a septicemia and because death had occurred from bronchopneumonia in some of the cases reported. Sedation was used to control convulsions, but it was used cautiously so that additional central nervous system depression would not be superimposed on that which might be due directly to the boric acid.

*Boron Content of Tissues*

| Tissue | Boron, Mg./Gm. | As Boric Acid, Mg./100 Gm. |
|---|---|---|
| Brain | 0.24 | 137 |
| Liver | 0.29 | 165 |
| Kidney | 0.28 | 160 |
| Heart | 0.22 | 125 |
| Thymus | 0.37 | 201 |
| Muscle | 0.34 | 194 |
| Fat | 0.03 | 17 |
| Whole blood | 0.21 | 120 |
| Serum | 0.20 | 114 |

## COMMENT

*Acute Toxicity.*—In experimental animals the toxic dose has been investigated by several persons, with somewhat variable results, because of the difference among species, in the method of reporting (such as minimum lethal dose, median lethal dose), and in the method and rate of administration of the drug. Buzzo and Cerratola [1] state that rabbits died of central paralysis and gastrointestinal irritation after doses of 4 gm. per kilogram. They also state that Gaucher found the toxic dose to be 1 gm. per kilogram in guinea pigs. Negri [2] states that the minimum lethal dose in rabbits is 0.043 gm. per kilogram. In a brief note McIntyre and Burke [3] state that amounts comparable to that received intravenously by their patient who recovered when given to dogs and rats caused no visible toxic symp-

1. Buzzo, A., and Cerratola, R. D.: The Toxicity of Boric Acid and of Borates Used as Preservatives and Antiseptics, Rev. Asoc. méd. argent. **46**:1493, 1932; cited by Ross, C. A., and Conway, J. F.: The Dangers of Boric Acid, Am. J. Surg. **60**:386, 1943.

2. Negri, G.: On the Distant Toxicity of Boric Acid, Rassegna di terap. e pat. clin. **1**:472, 1929; cited by Ross, C. A., and Conway, J. F.: The Dangers of Boric Acid, Am. J. Surg. **60**:386, 1943.

3. McIntyre, A. R., and Burke, J. C.: Intravenous Boric Acid Poisoning in Man, J. Pharmacol. & Exper. Therap. **60**:112, 1937.

toms (about 0.25 gm. per kilogram). The most thorough work on acute toxicity is that of Pfeiffer, Hallman, and Gersh.[4] They showed that the median lethal dose varies from 1.2 to 3.45 gm. per kilogram, with the guinea pig being more susceptible than mice and rats. The median lethal oral dose in dogs is about 2.0 gm. per kilogram and the median lethal subcutaneous dose about 1.0 gm. per kilogram.

The cases mentioned below are the only ones in the American literature in which the drug was ingested or given intravenously or subcutaneously to adults in single doses. The toxic dose for humans with single doses given orally or parenterally can be approximated from the following reports. Peyton and Green [5] report a man, age and weight not stated, who received 700 ml. of 4% boric acid (28 gm.) subcutaneously in error, with recovery. Marked symptoms developed, with vomiting, nausea, abdominal pain, confusion, and typical erythema. McIntyre and Burke's patient received 600 ml. of 2.5% boric acid in 10% dextrose (15 gm.) intravenously and had only a slight flush and nausea. Another adult, a 45-yr.-old woman, weight 135 lb. (61 kg.), was given 1 liter of 2% boric acid (20 gm.) subcutaneously, with only minimal symptoms.[6] Potter's patient,[7] a 66-yr.-old painter, took what was said to be about an ounce (30 ml.) of sodium borate by mistake and died within three hours. His stomach, however, still contained about 1½ oz. (45 gm.) at autopsy.

There are no data on the acute toxic dose for children. However, in McNally and Rust's [8] cases, six newborn infants, weight about 7 lb. (3,200 gm.), who were never described clinically, had received a single feeding of from 60 to 150 ml. of a saturated solution of boric acid (3 to 6 gm.) instead of water, and all died. Young, Smith, and MacIntosh [9] report six deaths in newborn infants following single feedings containing 1.7 and 1.25% boric acid. The amounts given are not stated, but if 3 to 4 oz. (90 to 120 ml.) were given, the amount of boric acid ingested must have been between 1 and 2 gm.

In all the other cases either the patients received smaller doses over longer periods or the dose was difficult to evaluate because of the method of absorption, e. g., irrigation, enemas, and dressings.

*Chronic Toxicity.*—One-tenth per cent of boric acid in the drinking water was without effect on normal growth of young rats, but 0.25% produced definite inhibition of growth in 20 to 30 days. Daily fluid intake was constant at 0.12 to 0.14 ml. per gram each dose. No characteristic lesions were found at autopsy, and there was no significant change in the blood during the experiment. Four dogs given 100 mg. of boric acid subcutaneously twice daily for 45 days showed no change in the peripheral blood.[4] It has been suggested that boric acid causes depression of bone-marrow activity when used to treat burns, but there seems to be no real evidence for this.

4. Pfeiffer, C. C.; Hallman, L. F., and Gersh, I.: Boric Acid Ointment: A Study of Possible Intoxication in the Treatment of Burns, J. A. M. A. **128**:266 (May 26) 1945.

5. Peyton, H. A., and Green, D.: Boric Acid Poisoning: Case Report, South. M. J. **34**:1286, 1941.

6. Brown, W. L.; Brown, C. P., and Murphy, J. L.: Toxicity of Boric Acid, J. A. M. A. **106**:1221 (April 4) 1936.

7. Potter, C.: A Case of Borax Poisoning, J. A. M. A. **76**:378 (Feb. 5) 1921.

8. McNally, W. D., and Rust, C. A.: The Distribution of Boric Acid in Human Organs in 6 Deaths Due to Boric Acid Poisoning, J. A. M. A. **90**:382 (Feb. 4) 1928.

9. Young, E. G.; Smith, R. P., and MacIntosh, O. C.: Boric Acid as a Poison: Report of 6 Accidental Deaths in Infants, Canad. M. A. J. **61**:447, 1949.

In humans boric acid may be used from several days [10] to several weeks [11] before the onset of acute symptoms. Forsyth [12] reports a celiac-like syndrome in an infant who had been given milk containing boric acid. The infant's celiac-like symptoms apparently cleared when the milk supply was changed.

*Absorption.*—When given intravenously, the drug obviously is distributed to the tissues rapidly. Brown, Brown, and Murphy [6] do not mention any local swelling or redness in their adult patient following subcutaneous injection of 1 liter of 2% boric acid, but Peyton and Green's patient had moderate swelling and tenderness of the thighs after receiving 700 ml. of 4% boric acid subcutaneously. It is fairly obvious that the drug is absorbed well when ingested. The median lethal oral dose in dogs, mice, and rats is about twice the subcutaneous or intravenous median lethal dose.[4]

Kahlenberg in 1924 [13] and again in 1928 [14] showed some absorption of boric acid through the intact skin. In both experiments the feet were immersed in containers of boric acid solutions, and the amount of boric acid which appeared in the urine was measured by a semiquantitative method using turmeric paper. When he used a solution of 450 gm. of boric acid in 6 liters of water and 3 liters of 95% alcohol, the maximum amount of boric acid in the urine was 0.005% at three to five hours. Using a saturated solution of boric acid in water, he found 0.0005% boric acid in the urine in 70 seconds and 0.001% within five minutes. However, Pfeiffer and co-workers were not able to demonstrate absorption through the intact skin using the turmeric-paper test on the urine. They used short-sleeved undershirts kept soaked in a saturated solution of boric acid and applied 10% boric acid ointment to the trunk as well as repeating Kahlenberg's method of soaking the feet in boric acid solution.

In man there have been a number of cases of intoxication and death following absorption through burned skin, eczema, or other open lesions.[15] Cope [16] examined the urine of 20 adults with severe burns who were treated with 10% boric acid ointment and found a maximum of 2.0 gm. of boric acid each 24-hr. collection of urine. When a saturated solution was used to irrigate the burns, as much as 2.5 gm. each day was excreted in the urine. No symptoms of boric-acid poisoning developed, and while Cope felt that these amounts were safe if renal function was normal, he did not recommend boric acid in the treatment of burns.

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10. Bazin, A. T.: Acute Boracic Acid Poisoning, Canad. M. A. J. **14**:419, 1924.

11. (*a*) Sanders, J. H.: Boracic Acid Poisoning, Brit. M. J. **1**:605, 1912. (*b*) McWalter, J. C.: Note on the Effects of Borax on Infants, Lancet **2**:369, 1907.

12. Forsyth, D.: Coeliac Disease or Boric Acid Poisoning, Lancet **2**:728, 1919.

13. Kahlenberg, L.: On the Passage of Boric Acid Through the Skin by Osmosis, J. Biol. Chem. **62**:149, 1924.

14. Kahlenberg, L., and Barwasser, N.: On the Time of Absorption and Excretion of Boric Acid in Man, J. Biol. Chem. **79**:405, 1928.

15. (*a*) Dopfer: On a Fatal Accident Following the Use of Official Ten Per Cent Boric Acid Ointment in a Burn, München. med. Wchnschr. **52**:763, 1905. (*b*) Savariaud, M.: In Serious Poisoning by Boric Acid Dressing, Foreign Letters (France), J. A. M. A. **63**:593 (Aug. 15) 1914. (*c*) Brose, L. D.: Death Following the External Use of Powdered Boric Acid, M. News, Philadelphia **43**:199, 1883. (*d*) Gissel, H.: Toxicity of Boric Acid, abstracted, Quart. J. Pharm. & Pharmacol. **6**:714, 1933. (*e*) Best, C. L.: Boric Acid Poisoning: Report of a Fatal Case with Autopsy, Tr. Chicago Path. Soc. **6**:161, 1903-1904. (*f*) Watson, E. H.: Boric Acid: Dangerous Drug of Little Value, J. A. M. A. **129**:332 (Sept. 29) 1945. (*g*) Abramson, H.: Fatal Boric Acid Poisoning in a Newborn Infant, Pediatrics **4**:719, 1949.

16. Cope, O.: The Treatment of Surface Burns, Ann. Surg. **117**:885, 1943.

Death has occurred from the use of boric acid solution in the treatment of widespread infantile eczema, and boric acid was found in the urine and cerebrospinal fluid in this case, reported by Watson.[15f] In spite of this, its use is still suggested by some.

Poisoning has occurred when boric acid solutions have been used in irrigations of the bladder,[11] when given as enemas,[17] and in irrigation of the pleural cavity in empyema.[18]

Boric acid is absorbed readily from the peritoneal cavity of dogs. Continuous irrigation of the abdominal cavity of two dogs with a 5% solution at the rate of 5 cc. a minute for three hours resulted in the retention of 31.0 and 34.7 gm. and a drop in the concentration of the perfusate to 1.5%.[4]

Pfeiffer and co-workers applied 10% boric acid to wounds and burns in dogs involving about 3% of the body surface. None of the dogs (three) died, but all showed large amounts of boric acid in the urine and in the tissues at autopsy after periods of 25 to 33 days.

*Excretion.*—In a few cases of poisoning it has been possible to follow the boric acid in the urine for varying periods. In McIntyre and Burke's patient, who received approximately 15 gm. intravenously, a total of 14.65 gm. ±0.71 gm. was recovered from the urine. The amount excreted became negligible at about 80 hr. Peyton and Green did not do quantitative studies of excretion in their patient, who had received 28 gm. subcutaneously, but they report a 4+ reaction for boric acid for three days with a gradual drop to 0 at seven days. Brown, Brown, and Murphy's patient (who received 20 gm. subcutaneously) showed a trace still present in the urine as late as the fourth day.

There is some evidence for cumulative action in some of the earlier cases reported in which acute symptoms did not develop until the patients had received boric acid for several weeks. Excretion is slow in man, apparently requiring several days for excretion of a single large dose, and this type of excretion also suggests that the poison well may be cumulative if single sublethal doses are repeated daily. Again, Pfeiffer and associates showed (1) that dogs excreted about 60% of a single dose in 48 hr.; (2) that when smaller daily doses were used, a period of 14 to 18 days was required before the urinary excretion reached a maximum and became constant, and (3) that appreciable amounts of boric acid were present in tissues for as much as four days after stopping the daily dose.

*Clinical Syndrome.*—A typical clinical picture usually begins with nausea, vomiting, abdominal cramps, and diarrhea. The gastrointestinal symptoms occur even though the boric acid enters the body by some other route. The vomiting may become very persistent, and the vomitus may contain blood. The stools may be bloody. An erythematous rash generally appears over most of the body and may involve the pharynx and tympanic membranes. There may be extensive exfoliation of the skin after several days. The reported conjunctivitis is probably due to vascular dilatation rather than a true conjunctivitis. In the severely poisoned patient shock develops, with fall in blood pressure, tachycardia, and cyanosis. The temperature is most frequently reported as being subnormal or as high as 101 F. (38.3 C.); however, Watson's patient had a temperature of 107 F. (41.7 C.), and in our case the temperature was 40.5 C. (104.9 F.) on admission, with a rapid

17. Bazin.[10] Sanders.[11a]

18. Ross, C. A., and Conway, J. F.: The Dangers of Boric Acid, Am. J. Surg. **60**:386, 1943.

fall prior to death. Shortly after the onset of poisoning the patient may become delirious, stuporous, and comatose. Convulsions are frequent, and death appears to be due to central nervous system depression in those persons who survive the initial shock.

Death may be due to shock early in the disease. The mechanism of the peripheral vascular dilatation and shock is not known. The most important effects seem to be on the central nervous system, with coma, convulsions, and death from central nervous depression or shock. In several cases and in Pfeiffer's experimental animals signs of meningismus are described. In several cases death has occurred some time after poisoning and apparently after all the boric acid had been excreted. Watson's patient died three weeks after poisoning without regaining consciousness; no boric acid had been detected in the urine after the first week, and no boric acid was found in the tissues at autopsy. One of the four newborn infants who died in a New London Conn., nursery survived for 11 days after the last dose of boric acid, and no boron could be detected in the liver at autopsy. The six deaths in infants reported by Young, Smith, and MacIntosh occurred from 19 hr. to five and one-half days after ingestion of a single oral dose. It would appear that if extensive enough, the damage done to the tissues by boric acid is irreversible even though the boric acid is eventually excreted.

In reviewing the reported cases of boric-acid poisoning, the most characteristic findings are the gastrointestinal symptoms and the typical erythematous rash. In the more severely poisoned patient there are a superimposed shock-like picture and severe central nervous system involvement. The diagnosis may be further substantiated by the demonstration of boric acid in the urine by the turmeric-paper test or by the spectrographic method.

*Clinical Laboratory Observations.*—Unfortunately, very few metabolic or chemical observations have been made in cases of boric-acid poisoning. No tests of liver function have been made, except for Peyton and Green's observations that there was no rise in the icterus index. There is evidence of renal damage which may be a direct effect of boric acid or secondary to shock, as indicated by reports of albuminuria and elevation of the blood urea nitrogen or blood nonprotein nitrogen. No reports are available of electrocardiographic changes. There are no abnormalities of the peripheral blood cells, but no work has been done on possible defects in the clotting mechanism.

Values for plasma electrolytes have been recorded very infrequently. Peyton and Green report low blood chloride levels but nothing else. In our case the carbon dioxide–combining power was 23.6 mEq. per liter (52 vol. %) and serum chloride 103 mEq. per liter (602 mg. per 100 cc. NaCl). These confirm the experimental findings of Pfeiffer and associates, who found no significant changes in the blood electrolytes of dogs receiving 1.0 gm. of boric acid per kilogram. They do report that intravenous doses resulted in a fivefold increase in phosphorus excretion in one to two hours, but they found no change in plasma lipid and inorganic phosphorus.

*Pathological Findings.*—Pathological findings reported by others agree rather well with our findings. In some cases edema of the brain with flattening of the convolutions is mentioned,[19] and while the brain in our case was heavier than

19. Grant, R. S., and Wegner, E. S.: Fatal Case of Boric Acid Poisoning, Am. J. Dis. Child. **75**:910 (June) 1948. Opper, L. S., in discussion on Pfeiffer, Hallman, and Gersh.[4] Young, Smith, and MacIntosh.[9]

normal, it did not appear to be edematous. Varying degrees of hemorrhagic enteritis are common findings, as are degenerative changes in the liver, characterized by cloudy swelling and in some cases central necrosis. The reported renal pathological changes vary a great deal from questionable cloudy swelling of the tubules to advance degeneration. Microscopic findings in the skin are limited to epidermis and are edema, degenerative changes in the keratin, and desquamation. No consistent or marked changes have been found in the spleen, adrenals, pancreas, heart, bone marrow, or lymphoid tissue.

It should be emphasized that with the exception of the excoriation and desquamation of the epidermis and the hemorrhagic enteritis, the pathological findings can all be secondary to profound shock.

Pathological findings in the brains of dogs were correlated with the dosages given but not with the concentration of boron in the brain at death. The microscopic findings in the brain and spinal cord consisted of varying degrees of round-cell infiltration and hyperchromatism and vacuolization of the neurons.[4] Distribution and concentration of boric acid, as indicated by separate tissue analysis, are variable, evidently depending on the dose and the time interval between the last dose and tissue analysis. In most cases the concentration is higher in the brain than in other tissues.

*Treatment and Prevention.*—There is no known specific treatment for boric-acid poisoning. Our reviews of the literature revealed no reports on the clinical or experimental use of dimercaprol (BAL) in the treatment of boric-acid poisoning. Pfeiffer, Hallman, and Gersh report that the use of plasma and a saline solution (solution of three chlorides) is of some value in treating the shock which occurs in boric-acid poisoning, but there is nothing to suggest that this is at all specific. In some of the cases reported it would appear that the treatment of the shock was inadequate.

At present all that we can offer is symptomatic therapy, including intravenous administration of fluids and plasma or blood, antibiotics, and possibly adrenal cortical extracts.

Since boric acid is used frequently for various therapeutic purposes and since relatively few deaths have been reported in the literature, it would appear that lethal quantities are found only when it is ingested accidentally, administered parenterally, or applied to a previously injured or diseased skin surface. The therapeutic value of boric acid is doubtful and its antiseptic quality minimal. There are better and safer substances available for uses as antiseptics, irrigations, wet dressings, and ointments. For this reason, boric acid or boric acid solutions have not been stocked on any of the floors, nurseries, or treatment rooms of Strong Memorial Hospital or Rochester Municipal Hospital.

## SUMMARY

A report of a fatal case of boric-acid poisoning in a 9-mo.-old infant, including laboratory and autopsy findings, is given, with a review of the literature, a discussion of boric-acid poisoning, and a discussion of the treatment of boric-acid poisoning.

# Abstracts from Current Literature

## Metabolism; Infant Feeding; Milk and Other Foods

PROTEIN REQUIREMENTS OF INFANTS. W. F. YOUNG, E. A. BISHOP, EVELYN M. HICKMAN, and YVONNE J. WILLIAMS, Arch. Dis. Childhood **24**:262 (Dec.) 1949.

Observations have been made on 79 infants suffering from marasmus who weighed 80% or less of the expected weight before treatment. The cause of the wasting was diagnosed and treated, and efforts were made to improve nutrition without delay. Hydrolyzed casein was used to augment the protein intake in the early stages of graded feeding, and later undiluted cows' milk mixtures were substituted. The feedings were arranged to provide about 120 cal. and 6 gm. of protein per kilogram per day throughout treatment.

Progress was assessed by the rate of gain in weight, and recovery appeared to be made earlier and to proceed more regularly than before. If infection was present, it sometimes did and sometimes did not retard the rate of recovery.

The serum protein and hemoglobin levels were estimated at weekly intervals for the periods during which the patients remained under hospital care. The changes in the serum protein levels were irregular but were sometimes found to be similar to those which have been described for animals and for adult humans during periods of recovery from starvation and protein depletion. Severe hypoproteinemia and anemia were seldom found.

Many weeks may elapse before a wasted infant attains a good nutritional status. During this time special care is needed to insure that he receives an optimum diet until his weight reaches the normal range for his age and to prevent exposure to infection.

KELLY, Milwaukee.

PROBLEMS OF FEEDING NORMAL CHILDREN DURING INFANCY AND CHILDHOOD. L. K. MITRA, Indian J. Pediat. **18**:74 (April) 1950.

This article deals briefly with the routine feeding of infants.

McGUIGAN, Evanston, Ill.

GENERAL COMPOSITION AND VITAMIN CONTENT OF THE POLLEN GRAIN OF THE DATE PALM, DACTYLIFERA PALMAE. L. M. S. RIDI and M. H. ABOUL WAFA, J. Roy. Egyptian M. A. **33**:168, 1950.

Analysis of date pollen shows that it contains more protein than meat, as much sucrose as sugar cane, more calcium and phosphorus than milk, more vitamin C than oranges and lemons, and more riboflavin than eggs.

McGUIGAN, Evanston, Ill.

## Prematurity and Congenital Deformities

PREMATURE INFANTS IN A SWEDISH COUNTY HOSPITAL: FREQUENCY AND EARLY PROGNOSIS. KJELL L. MÖLLER, Acta pædiat. **39**:102, 1950.

The author analyzes and discusses a 10-yr. series of 952 premature live births from a Swedish district hospital where the percentage of premature births was 5.4. The author shows that multiple births are partly responsible for prematurity and that the mothers of premature infants are more frequently unmarried. The total mortality at the hospital was 21.6%, the death rate being 12.3% for the first day and 17.9% for the first week. The death rate of boys was significantly higher than that of girls. Obstetric intervention did not increase mortality, probably because in intervention cases the infants' birth weights were higher. The mortality rate of the infants of mothers with nephropathia gravidarum seemed lower, presumably because of longer intrauterine life.

The author also reports 176 premature stillbirths from the same period, but with a weight distribution different from that of the live births and a lower percentage of multiple births. The

mothers in stillbirths were relatively older and more frequently married. Nephropathia gravidarum was present in the mothers in 22.7% of the stillbirths.

Finally, the results are compared with the figures of earlier material. The author recommends standardization of relevant definitions and registration methods so that the true prognosis of the premature may be established and the efficacy of modern therapeutic measures judged. Ylppö's nomenclature is recommended.

FROM THE AUTHOR'S SUMMARY.

## Newborn

PNEUMOTHORAX IN THE NEWBORN INFANT. JAMES E. STRAIN and JOHN R. CONNELL, J. Pediat. **36**:495 (April) 1950.

Strain and Connell review the literature and report an additional case of this unusual disorder. In their patient a bilateral pneumothorax developed at the age of 4 days. The diagnosis was made by roentgenography. The patient was given oxygen and carbon dioxide inhalations and recovered.

MACDONALD, Pittsburgh.

SALMONELLA MENINGITIS IN THE NEWBORN. D. C. METCALFE and G. B. WISWELL, Canad. M. A. J. **62**:500 (May) 1950.

A case of meningitis due to Salmonella typhimurium in an 11-day-old infant is reported. Treatment with streptomycin and sulfadiazine was continued over a period of 110 days. Two months after discharge the infant appeared normal in every respect. This case appears to be the only one due to this organism in which there was recovery and the second due to any Salmonella in which an infant under 1 mo. has recovered.

MCGUIGAN, Evanston, Ill.

MILIARY SEBACEOUS CYSTS AND BLISTERS IN THE HEALTHY NEWBORN. ISRAEL GORDON, Arch. Dis. Childhood **24**:286 (Dec.) 1949.

Approximately 40% of healthy newborn infants present milia, mainly on the face. These milia are miliary sebaceous cysts and blisters and have probably resulted from the epidermis overgrowing the ducts of sebaceous glands. In fetal life the sebaceous glands are highly active, perhaps to help to form the vernix caseosa. The incidence of these cysts and blisters gradually diminishes and becomes negligible by the second three months of life. There may be some relation between activity of these sebaceous glands and cholesterol metabolism.

KELLY, Milwaukee.

SOME REMARKS ON THE MICROSCOPIC STRUCTURE OF THE PLACENTA IN ERYTHROBLASTOSIS. A. L. C. SCHMIDT, Maandschr. kindergeneesk. **18**:156, 1950.

Schmidt arrives at the conclusion that the cause of the changes in the placenta in erythroblastosis must be ascribed not only to the influence of the child but also to the reciprocal influence of the chorial tissue and the maternal environment.

FROM THE AUTHOR'S SUMMARY.

## Acute Contagious Diseases

PAIN AND CONTRACTURE IN POLIOMYELITIS. ARTHUR C. GUYTON and ROBERT C. REEDER, Arch. Neurol. & Psychiat. **63**:954 (June) 1950.

The authors attempted to reproduce in dogs the muscle pain and contracture noted in poliomyelitis. It was found that anterior rhizotomy reproduced these conditions to a remarkable degree. The pain and contracture are apparently due to changes induced by denervation of the muscle.

MCGUIGAN, Evanston, Ill.

ORCHITIS IN THE COURSE OF SEVERE CHICKEN POX WITH PNEUMONITIS, FOLLOWED BY TESTICULAR ATROPHY. CONRAD WESSELHOEFT and C. M. PEARSON, New England J. Med. **242**:651 (April 27) 1950.

The authors add a second case of orchitis and epididymitis during the course of chickenpox in an adult to the one case extant. The patient was 46 years old and his chickenpox was compli-

cated not only by orchitis, epididymitis, and testicular atrophy but also by a miliary pneumonic dissemination of the virus, with a resultant viral pneumonia which resisted penicillin and streptomycin treatment. The visceral and neurologic manifestations of chickenpox are described.

WHEELOCK, Denver.

SERUM MUCOPROTEINS IN CHILDREN IN HEALTH AND DISEASE WITH SPECIAL REFERENCE TO RHEUMATIC FEVER. VINCENT C. KELLEY, ROBERT A. GOOD and IRVINE MCQUARRIE, Pediatrics **5**:824 (May) 1950.

Serum mucoprotein levels were determined in 125 normal subjects and in 207 patients suffering from a wide variety of diseases. Mucoprotein levels in normal children were found not to differ significantly from those of normal adults, and no significant variation with age was found among children. Subnormal levels of mucoproteins were found invariably in the serum of patients with lipid nephrosis. Marked elevations were found in generalized malignancy, in some cases of acute bacterial and viral infections, in rheumatoid arthritis, and in active rheumatic fever in children. Normal or but slightly elevated serum mucoprotein levels were found in children with uncomplicated Sydenham's chorea, in those with rheumatic fever in the inactive phase, and in nonrheumatic children with uncomplicated acute streptococcic pharyngitis. In rheumatic fever elevations in the level of serum mucoproteins were found to parallel the degrees of activity of the disease process.

FROM THE AUTHORS' SUMMARY.

CASE FATALITY IN INFANTS AND CHILDREN WITH PERTUSSIS, 1942-1946. JEROME L. KOHN, ALFRED E. FISCHER and HERBERT H. MARKS, Pediatrics **5**:840 (May) 1950.

Analysis of data on patients with pertussis during 1942 to 1946 obtained by means of a questionnaire from communicable-disease hospitals and from health officers in a number of cities in the United States and Canada showed these results:

Case fatality rates of patients admitted to hospitals for treatment have declined substantially in the period under review. This decline is general, both among infants under 1 yr. of age and among older children. In 1946 the case fatality rate of the infants hospitalized for the disease was 4.6% in those cities for which data for at least four years were available. This may be compared with the rates of 7.8% in 1942 and 11.1% in 1943. For ages 1 yr. and over the rate was only 1.3% in 1946, as compared with 1.7% in 1942 and 3.7% in 1943. The rates in the hospitals with larger experiences were generally more favorable than in hospitals with smaller experiences.

Despite the incomplete reporting of pertussis, which results in exaggerating the case fatality rate for the general population, the level of these rates in the community as a whole was lower than for hospitalized patients. This reflects the higher proportion of the severer cases in the hospitalized group. Indications are that in many places hospitalization is limited more and more to severe cases.

Progress in the management of pertussis, especially in the severer cases with hospital admission, is believed to be the chief factor in the decline in case fatality of pertussis.

A request contained in the questionnaire for an opinion on the severity of pertussis during the period studied elicited few replies, and these replies showed a division of opinion on the matter. It appears unlikely that there has been much of any change in the severity of the disease.

FROM THE AUTHORS' SUMMARY.

CONVULSIONS AND HEMIPLEGIA IN PERTUSSIS PROPHYLAXIS. H. B. GRACE, Canad. M. A. J. **63**:128 (Aug.) 1950.

Two cases are reported of severe convulsions with postconvulsive sequelae occurring after injections of triple antigens containing pertussis vaccine. Both children had histories of convulsions. The author feels that the pertussis vaccine was responsible and warns against its use in children of known convulsive tendencies.

MCGUIGAN, Evanston, Ill.

BLOOD PICTURE IN EXANTHEMA SUBITUM WITH SPECIAL REFERENCE TO THE FIRST PHASE. C. SAAL, Helvet. paediat. acta **5**:291 (June) 1950.

The blood picture in 50 cases of exanthema subitum was studied during the first phase of the illness. During the first three febrile days the blood showed a moderate leucopenia and

pronounced neutrophilia, lymphopenia and monocytosis. The characteristic blood picture does not develop until the fourth day; that is, leucopenia, neutropenia, relative lymphocytosis, and a normal number of monocytes.

FROM THE AUTHOR'S SUMMARY.

PENICILLIN IN THE TREATMENT OF DIPHTHERIA. FLORENCIO BAZÁN, ELIAS SCHTEINGART, and L. RODRIGUEZ GAETA, Pediat. Américas **8**:1 (Jan.) 1950.

Since 1945 the authors have been using antitoxin and penicillin in the treatment of diphtheria. They report their results with 61 patients, 12 of them with "malignant diphtheria," 33 with a "serious form" of diphtheria and 16 with diphtheritic laryngitis. The mortality rate was 83.3% for the first group, 12.1% for the second, and 20.36% for the third. Penicillin was used in amounts that varied between 10,000 and 40,000 units intramuscularly every three hours. The total dose was 300,000 to 2,000,000 units.

Comparing the results obtained with those which they had before in the same service but without penicillin, the authors conclude that penicillin did not help to improve the complications and mortality in this series of patients with diphtheria.

DE LA TORRE, MÉXICO D. F.

EPIDEMIOLOGY OF INFANTILE PARALYSIS IN THE WESTERN HEMISPHERE: I. VÍCTOR ESCARDÓ Y ANAYA, Bol. Inst. internac. Am. Protec. infancia **24**:7 (March) 1950.

The author makes a comparative study of the epidemics of infantile paralysis in the Western Hemisphere. This first part comprises data from Central and South America. He reviews the general aspects, without going into details, to see if it is possible to establish some bond or relation between the progress of the illness in the different countries. To this end he presents the morbidity and case fatality rates, with data obtained from the best available sources, but presented provisionally, so that, by verifying or correcting these data it should be possible to reach really valid conclusions.

FROM THE AUTHOR'S SUMMARY.

CONTRIBUTION TO THE HISTORY OF POLIOMYELITIS. QUECKE, Med. Klin. **25-26**:807 (June 23) 1950.

In a previous article W. Hellermann described an early Egyptian relief from about 1,500 B. C. as the first certain delineation of poliomyelitis. In the present article attention is called to the fact that pes equinus is not exclusively pathognomonic for poliomyelitis.

AMBERG, Rochester, Minn.

OBSERVATIONS ON AN OUTBREAK OF RUBEOLA AMONG TUBERCULOUS CHILDREN. HEINZ DUSCHL, Monatsschr. Kinderh. **97**:338 (Oct.) 1949.

Forty-seven patients with tuberculosis in whom rubeola developed were studied. Intense sweating and marmoration of the skin before the eruption were noted. Plasmocyte counts were never over 11%. The shortest incubation period was 11 days. No influence on the tuberculous process was noted in any of the patients, but in five children intracutaneous tuberculin reactions which previously had been positive became temporarily negative.

HARTENSTEIN, Madison, Wis.

PRODROMAL ILLNESSES DURING THE BERLIN POLIOMYELITIS EPIDEMIC OF 1947. GERHARD JOPPICH, and FRITZ KUSKE, Monatsschr. Kinderh. **97**:343 (Oct.) 1949.

Of 2,246 cases of poliomyelitis, a history of prodromal illness was elicited in 1,170 cases (52%). Six hundred and fifty-two patients had symptoms referable to the respiratory tract, 218 referable to the gastrointestinal tract. Twenty-two patients had specific infectious diseases, and 82 gave a history of external injury or trauma. Eighty-two cases had a combination of all of these. There was no relationship between these illnesses and the localization of paralysis, season, or age. It is believed that the great majority of the prodromal diseases were caused by the virus of poliomyelitis, although not representing the time of invasion of the virus.

HARTENSTEIN, Madison, Wis.

CUTANEOUS-ALLERGIC REACTIONS WITH ANTIGENS OF THE VACCINE-VARIOLA GROUP. K. MEGAY, Wien. klin. Wchnschr. **62**:404 (June 9) 1950.

The allergy test proposed by Tieche more than 30 years ago is discussed. The test is carried out on a person highly allergic to cowpox virus, responding to vaccination with a pronounced early reaction. Such a person responds similarly to scarification with material from smallpox and alastrim, probably a less violent type of variola, also with an early reaction, within two to six hours, but not to scarification with material from paravaccinia or milkpox. The material used for the test is usually diluted with glycerin and does not lose its activity on heating to 100 C. The reaction may be delayed somewhat, particularly in persons of lower sensitivity.

AMBERG, Rochester, Minn.

PROCAINE PENICILLIN THERAPY IN SCARLET FEVER. TORBEN JERSILD and JOHN MUNCK, Acta pædiat. **39**:57, 1950.

The material comprises 200 scarlatinal patients to whom penicillin procaine was administered intramuscularly for six days, the dosage being 120,000 to 300,000 units once daily. All the patients were under ambulatory follow-up observation for at least six weeks.

On admission 69.5% of the patients showed a growth of hemolytic streptococci. After 24 hr. of treatment with penicillin procaine hemolytic streptococci were found in only 3% of the cases, and upon discontinuance of the treatment, in 1.5%.

Thus the effect on the bacteriological status in scarlet fever as indicated by the outcome of the cultures is fully equal to the effect obtained with ordinary penicillin given twice a day.

The frequency of more serious complications is no higher for treatment with penicillin procaine than for treatment with ordinary penicillin. No instance of nephritis or mastoiditis was seen in this material.

None of the patients presented any local or general by-effects from the treatment.

FROM THE AUTHORS' SUMMARY.

## Acute Infectious Diseases

SEPTICEMIA IN INFANCY. JOHN J. KANGOS, Arch. Pediat. **67**:99 (March) 1950.

The author presents 11 cases of sepsis in infancy. Eight postmortem examinations were made, and congenital anomalies were found in three cases, or 37.5%. Kangos then reviews other published series in which congenital anomalies were found in 27% and 35% of the infants autopsied. He theorizes that the occurrence of anomalies in these cases in indicative of the presence of stunted developmental processes in these infants. This might perhaps explain their vulnerability to infection.

DAVIS, Denver.

ANTIRHEUMATIC ACTIVITY OF ASCORBIC ACID IN LARGE DOSES: PRELIMINARY OBSERVATIONS ON SEVEN PATIENTS WITH RHEUMATIC FEVER. BENEDICT F. MASSELL, JOSEPH E. WARREN, PAUL R. PATTERSON and HAROLD J. LEHMUS, New England J. Med. **242**:614 (April 20) 1950.

The authors have treated seven children with rheumatic fever with large doses of ascorbic acid since Jan. 2, 1950. The dose was 1.0 gm. of ascorbic acid four times a day for from eight to 26 days. Four children were still receiving treatment on March 20, 1950. The rheumatic manifestations involved ranged from polyarthritis to congestive failure.

Symptoms and signs of rheumatic activity have, in general, reverted to normal or near normal levels within an unusually short time, although the sedimentation rate has not returned to normal in the majority of cases.

The historical background for the use of ascorbic acid in rheumatic disorders is briefly presented, and a note of warning is sounded to prevent premature comparison with other methods and unfounded conclusions.

WHEELOCK, Denver.

THE CLINICAL RESPONSE OF RHEUMATIC FEVER AND ACUTE CARDITIS TO ACTH. BENEDICT F. MASSELL, JOSEPH E. WARREN, GEORGE P. STURGIS, BUFORD HALL and ERNEST CRAIGE, New England J. Med. **242**:692 (May 4) 1950.

Corticotrophin (ACTH) was administered for periods of 10 days to 14 weeks to 10 patients with active rheumatic fever. Most of the important manifestations of rheumatic fever were

represented by these 10 patients. The majority of the patients were severely ill and suffered from a high degree of active carditis.

In general, the clinical response was satisfactory in all but 1 of the 10 patients, but the speed and extent of the response varied considerably. In the light of previous experience at the House of the Good Samaritan, Boston, the improvement shown by the majority of the patients was striking. In spite of transient withdrawal reactions encountered in some cases at the end of therapy, the rheumatic process finally subsided within four to 10 weeks in five of eight patients who were followed for periods of one to four months after the completion of treatment. In one of the remaining three patients the response was slower, although a state of quiescence was finally attained. Another very ill patient improved considerably but still has low-grade, active rheumatic fever. In the third patient there is no definite evidence that corticotrophin was responsible for any improvement. Definitely significant systolic or diastolic murmurs, or both, regressed in three cases, and in two of these (both early cases) the auscultatory signs completely disappeared within three to 10 weeks.

Corticotrophin therapy seems to have two opposing actions in patients with active rheumatic carditis and congestive failure. A tendency of the hormone to cause retention of fluids may result in an aggravation of the latter condition. On the other hand, suppression of the active rheumatic process and consequent improvement in the myocardium tends in the long run to relieve congestion. In cases in which corticotrophin caused an accumulation of fluids, congestive failure could be controlled by a low-sodium diet and mercurial diuretics.

In addition to increase in previously existing congestive failure, the only other important untoward reaction to corticotrophin therapy was the development of severe mental depression in one patient. Minor side effects have been abdominal cramps, headache, and the development of roundness of the face, acne, and skin striae.

Although no final conclusions regarding optimum dosage of corticotrophin can be drawn from this small series of cases, it appears that the minimal effective individual dose may be between 5 and 10 mg. and the minimum daily dose between 20 and 50 mg.

Corticotrophin probably acts by causing an increased endogenous production of 11,17-oxysteroids by the adrenal cortex, but the mechanism by which the adrenocortical steroids in turn suppress the active rheumatic process is not known. FROM THE AUTHORS' SUMMARY.

TWO CASES OF COLITIS FROM LAMBLIA INTESTINALIS. F. MORABITO, Lattante **21**:100 (Feb.) 1950.

Two children had colitis with mucus and blood in the stools. Fecal examinations revealed many Giardia lamblia (Lamblia intestinalis) parasites. Acetarsone and acridine derivatives were effective in relieving the condition.

HIGGINS, Boston.

CASES OF VISCERAL LEISHMANIASIS IN CHILDREN SEEN IN THE DECENNIUM 1939-1949 IN THE PROVINCE OF BRINDISI. E. ZAMBRANO, Lattante **21**:283 (May) 1950.

Twenty-one cases of kala-azar were proved by the finding of the parasites on splenic puncture in the 10 year period. The patients consisted of 11 girls and 10 boys, and all but three were between 1 and 5 years of age. The time of onset of symptoms was well distributed throughout the year. One village was the main center of the contagion.

HIGGINS, Boston.

TREATMENT OF ENTEROBIASIS VERMICULARIS WITH GENTIAN VIOLET. W. WARNECKE, Med. Klin. **45**:737 (June 9) 1950.

Fourteen patients, seven of whom were children, were treated with methylrosaniline chloride (gentian violet) from two different sources without striking results.

AMBERG, Rochester, Minn.

SPECIFIC TREATMENT OF INFECTIOUS DISEASES WITH SPECIAL CONSIDERATION OF TRANSFUSION WITH RECONVALESCENT BLOOD. H. VON LOBENSTEIN, Med. Klin. **45**:770 (June 16) 1950.

This short paper refers, without any detail, to the author's favorable experience with the transfusion of convalescent whole blood in cases of exanthematous typhus when convalescent

serum was not successful. Furthermore, he refers to good results in cases of severe toxic scarlet fever. Good results are mentioned in cases of typhoid and paratyphoid fever. Transfusion of the mother's blood and intramuscular injections of such blood was given to a child severely ill with poliomyelitis after appearance of paralysis with complete recovery resulting. In cases of poliomyelitis, if no convalescent blood is available, blood of the mother or of normal persons may be given.

AMBERG, Rochester, Minn.

TETANUS AND ATELECTASIS OF THE LUNG DUE TO ASPIRATION OF GARDEN SOIL IN A BOY OF SEVENTEEN MONTHS. OLE CHRISTENSEN, Acta pædiat. **39**:170, 1950.

A report is given of a case of tetanus and complete atelectasis of one lung due to aspiration of garden soil in a boy 17 mo. old. The atelectasis subsided spontaneously after having persisted for at least 18 days. The tetanus was cured.

It is emphasized that a number of cases of tetanus in childhood make their appearance without any noticeable external injury, and that this fact ought to be looked upon as an additional argument in favor of general employment of vaccination against this disease.

FROM THE AUTHOR'S SUMMARY.

## Chronic Infectious Diseases

THE TREATMENT OF MILIARY TUBERCULOSIS WITH STREPTOMYCIN. HARRY R. LITCHFIELD, S. DAVID STERNBERG, and BERNARD D. ZALEZNAK, Arch. Pediat. **67**:157 (April) 1950.

The authors briefly review the treatment of miliary tuberculosis and tuberculous meningitis with streptomycin, thiazole sulfone (promizole®) and paraaminosalicylic acid. They then report the treatment of a 12-mo.-old Negro girl admitted to the hospital in extremely poor condition with miliary tuberculosis. She was treated for 90 days with streptomycin. The cultures for tubercle bacilli were negative; lumbar punctures gave normal results. After 90 days of treatment she was discharged in apparently good condition, having gained 3 lb. (1.3 kg.), and the x-ray signs of miliary tuberculosis had cleared. Two months later she was admitted to a contagious-disease hospital with what was thought to be clinical poliomyelitis. After she had recovered from this, findings consistent with tuberculous meningitis developed, and at the time of publication of the article, she was under vigorous treatment for this. The authors emphasize that a prognosis cannot be made upon the basis of results immediately following the therapy.

DAVIS, Denver.

RECENT DEVELOPMENTS IN THE DIAGNOSIS OF CONGENITAL HEART DISEASE. NELSON K. ORDWAY, RICHARD L. BAGUETTE, ALBERT L. HYMAN, and LOUIS LEVY, New Orleans M. & S. J. **103**:1 (July) 1950.

The use of arterial puncture and venous catheterization is discussed, and their application to diagnosis of various congenital cardiac defects is illustrated.

McGUIGAN, Evanston, Ill.

A STUDY OF TEN CHILDREN AFTER TREATMENT WITH STREPTOMYCIN FOR TUBERCULOUS MENINGITIS. JOHN LORBER, Arch. Dis. Childhood **24**:289 (Dec.) 1949.

The physical and mental state and the emotional pattern of 10 children successfully treated with streptomycin for tuberculous meningitis have been analyzed. All the children are now at home and have been followed for at least 10 months from the beginning of treatment, and for four to 16½ months after the treatment completed by the end of May, 1949.

All the children are in good physical health and are normal mentally. There is no evidence that the illness has caused any difference in their general behavior. The intelligence quotients are within the normal range of variation.

The only neurological after-effect is deafness in one case.

All the children were alive and well at the end of July, 1949, after a minimum observation period of one year from the beginning of treatment.

KELLY, Milwaukee.

CONGENITAL TOXOPLASMOSIS: A REPORT OF TWO CASES. JAMES H. HUTCHINSON, Arch. Dis. Childhood **24**:303 (Dec.) 1949.

The etiology, pathology, clinical and serological diagnosis, and prognosis of congenital toxoplasmosis are briefly reviewed. Two probable cases occurring in the United Kingdom and not noted in the literature are described and discussed.

KELLY, Milwaukee.

LABORATORY DIAGNOSIS OF TUBERCULOUS MENINGITIS. G. H. ROBERTSON and I. BERSOHN, South African M. J. **24**:411 (June 3) 1950.

A review of spinal fluid findings in 104 cases of tuberculous meningitis is presented. The author stresses the fact that cellular, chemical changes or a combination of the two is diagnostic, and the search for acid-fast bacilli must be intensified, since it is the surest diagnostic measure.

McGUIGAN, Evanston, Ill.

TUBERCULOSIS OF MECKEL'S DIVERTICULUM. S. LEVIN, South African M. J. **24**:496 (June 24) 1950.

An unusual case of tuberculosis of Merckel's diverticulum in a 3-yr.-old native child is presented. The child was known to have generalized tuberculosis.

McGUIGAN, Evanston, Ill.

THE ADRENALS AND TUBERCULOSIS. RUDOLF ABDERHALDEN and GERTRUD ABDERHALDEN, Bull. schweiz. Akad. med. Wissensch. **6**:48 (March) 1950.

The authors examined 302 patients with pulmonary tuberculosis to check the presence of functional disorders of the adrenals and the presence of proteinases in the urine capable of hydrolyzing the proteins of Mycobacterium tuberculosis. It was shown that a disturbance of the cortex of the adrenals exists in nearly all severe cases. Only 36% of the patients with mild tuberculosis had a disturbance of the adrenal cortex. There was no disturbance of the medulla of the adrenals. In confirmation of earlier researches, it was found that only 80% of the patients with pulmonary tuberculosis excrete an enzyme with their urine which hydrolyzes the proteins of Mycobacterium tuberculosis.

FROM THE AUTHORS' SUMMARY.

ACTIVATION OF TUBERCULOUS PROCESSES IN CHILDHOOD AFTER BRONCHOGRAPHY. HARALD SAAME, Med. Klin. **45**:764 (June 16) 1950.

A 4-yr.-old girl, with the diagnosis of bilateral bronchial lymph gland tuberculosis, was subjected to bronchography with iodized oil (iodipin®) on suspicion of bronchiectasis. The bronchogram was normal. About six weeks later infiltrations were demonstrated in the right middle and left lower field, regressing slowly in the next four months. An activation by the iodized oil bronchography is regarded as probable.

A 14-year-old girl was admitted with probable hematogenous tuberculous lesions in the lungs. A small cystic degeneration was suspected, and a bronchogram of the right middle field was made, with negative results. Another bronchogram was made of the left upper and middle field. Nine days later fresh exudative foci were seen here leading to cavity formation. In this case the activation followed the iodized oil administration immediately; hence a causative relation cannot be denied.

AMBERG, Rochester, Minn.

STREPTOMYCIN TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDHOOD. LORENZ, Wien. klin. Wchnschr. **62**:417 (June 16) 1950.

During a two-year period 33 patients with tuberculous meningitis were treated in the University Children's Clinic with streptomycin alone, or in combination with a sulfonamide drug, or with paraaminosalicylic acid. The combination with sulfonamides is not promising, but that with paraaminosalicylic acid is. Special stress is laid on early diagnosis, and the treatment must continue uninterruptedly for a sufficient period of time, not less than six months. The antibiotic must be given simultaneously intramuscularly and intraspinously. Without being too dogmatic,

the intramuscular injections are given twice daily in doses of 20 to 30 mg. per kilogram each day. The same dose for intraspinous injection is 1 to, at the most, 1.5 mg. per day and per kilogram daily for three months, and then as above for the intramuscular injections. Some of the untoward manifestations may be cited shortly. A 13-year-old boy became very obese, and his blood pressure became elevated. In two other boys psychotic symptoms developed and were present for a time.

AMBERG, Rochester, Minn.

## Diseases of Blood, Heart and Blood Vessels and Spleen

THE ELECTROCARDIOGRAMS OF ONE HUNDRED NORMAL INFANTS AND YOUNG CHILDREN. PATRICIA B. TUDBURY and DOROTHY W. ATKINSON, J. Pediat. **36**:466 (April) 1950.

The authors have studied the electrocardiograms of 100 children, ages 12 hours to 7 years. The results are recorded in this paper. The most striking observation is the fact that electrocardiograms in children vary widely.

MACDONALD, Pittsburgh.

CONGENITAL FAMILIAL HEMOLYTIC JAUNDICE. ISADORE COHN, New Orleans M. & S. J. **102**:484 (April) 1950.

Five cases of congenital hemolytic icterus in two generations of a single family are reported. All five patients were treated by splenectomy. Ages varied from 2 to 34 years. The author feels that while splenectomy does not change the typical findings in the peripheral blood, the patient goes along without marked evidence of hemolysis and may be considered greatly improved symptomatically. Accurate differentiation between acquired and congenital familial icterus is important, as the former is not benefited.

McGUIGAN, Evanston, Ill.

APPLICATION OF NEWER DIAGNOSTIC METHODS IN CONGENITAL HEART DISEASE. ALBERT HYMAN, LOUIS LEVY, RICHARD BAGUETTE, and NELSON ORDWAY, New Orleans M. & S. J. **103**:5 (July) 1950.

Diagnostic studies are presented, including cardiac catheterization in cases of patent ductus, interatrial septal defect, interventricular septal defects, and tetralogy of Fallot. The technique permits the magnitude of the shunt to be calculated in each case.

McGUIGAN, Evanston, Ill.

CONGENITAL MALFORMATIONS OF THE HEART AND GREAT VESSELS BENEFITED BY SURGERY. CHARLES J. MIANGOLARRA, New Orleans M. & S. J. **103**:10 (July) 1950.

Those defects remediable by surgery are briefly discussed. Short descriptions of these anomalies are given, together with principal diagnostic features. Coarctation of the aorta, vascular ring, patent ductus, and tetralogy of Fallot are included.

McGUIGAN, Evanston, Ill.

SERUM IRON AND IRON-BINDING CAPACITY OF THE SERUM IN CHILDREN WITH SEVERE MEDITERRANEAN (COOLEY'S) ANEMIA. CARL H. SMITH, THOMAS R. C. SISSON, WILLIAM H. FLOYD JR., and SHIRLEY SIEGAL, Pediatrics **5**:799 (May) 1950.

The blood of children with severe Mediterranean (familial erythroblastic) anemia was found to have a high serum iron and an absence of a latent or unbound iron capacity of the serum. Whereas serum iron levels comprise approximately one-third of the total iron-binding capacity in normal children and adults, the two values are equal in the severe form of Mediterranean anemia. The iron-binding capacity of the serum in this condition is therefore fully saturated and quantitatively lower than in normal children.

The absence of a measurable latent iron-binding capacity does not depend entirely on the liberation of iron from exogenously administered blood. Comparable changes were also noted in two nonanemic adult carriers possessing the trait of the disease, in two children with the mild form not requiring transfusions, and in one severely anemic child with Mediterranean

anemia who had never been transfused. Similar changes occurred in three patients with spherocytic anemia and in five children with sickle-cell anemia, one of whom had never been transfused.

In every instance, therefore, of the advanced form of Mediterranean anemia and in some of the nonanemic and mildly anemic forms of this disease, a fully saturated metal-binding protein is present in total amounts usually less than those found in normal children. In contrast, children with iron-deficiency anemia manifest a reduction in percentage saturation of iron-binding protein, an increased level of unbound latent iron-binding capacity, and a markedly elevated total iron-binding capacity.

The failure to demonstrate a latent iron-binding capacity of the serum in asymptomatic persons adds another criterion to those already established for the identification of carriers of the trait of Mediterranean anemia, who constitute the source of its transmission.

The presence of bilirubin in increased concentrations in the serum of patients with severe Mediterranean anemia does not interfere with its capacity to combine with iron. The capacity for binding iron was restored when Fraction IV-7 was added to samples of icteric serum of patients in whom no capacity had previously been demonstrated.

The high serum iron and absence of latent iron-binding capacity observed in children with severe Mediterranean anemia receiving multiple transfusions correspond to the changes regarded as diagnostic of transfusion hemosiderosis and hemochromatosis. While these changes remain unaltered in Mediterranean anemia, their reversibility has been demonstrated in two children with hemophilia who received weekly transfusions of small amounts of blood. After cessation of this form of therapy a decrease of serum iron and a gradual restoration of iron-binding capacity were noted.

FROM THE AUTHORS' SUMMARY.

A NEW PROTHROMBOPENIC DRUG, PHENYLINDANEDIONE. L. B. JAQUES, E. GORDON, and E. LIPP, Canad. M. A. J. **62**:465 (May) 1950.

The anticoagulant properties of 2-phenylindanedione-1,3 were studied. It appears to have a rapid anticoagulant effect but one of much shorter duration than that of bishydroxycoumarin. Peak effect is reached in 24 hr., and prothrombin time returns to normal in 14 hr., as compared with three days for bishydroxy coumarin. Single doses of the drug have little effect, but repeated doses result in prothrombin times as high or higher than those reached with bishydroxy coumarin.

McGUIGAN, Evanston, Ill.

THE DIAGNOSTIC VALUE OF CARDIAC CATHETERIZATION IN ISOLATED PULMONARY STENOSIS AND LARGE INTERVENTRICULAR SEPTAL DEFECTS. E. MANNHEIMER, Arch. Dis. Childhood **24**:264 (Dec.) 1949.

Isolated pulmonary stenosis is not a very rare type of congenital heart disease. Patients with this anomaly can live a normal life, and the prognosis seems to be remarkably good. The diagnosis is made entirely by cardiac catheterization. Idiopathic pulmonary dilatation as previously described may actually be isolated pulmonary stenosis with poststenotic dilatation.

Patent ductus arteriosus with enlarged heart and a large shunt, interauricular septal defects, and large interventricular septal defects often cannot be differentiated clinically. Cardiac catheterization gives the diagnosis in these cases. In many patients with septal defects between the ventricles there is equal pressure in both ventricles. In these, the septal defect is undoubtedly open during the systoles. In some other patients, also with large interventricular shunts, the pressure in the right ventricle is much lower than that in the left ventricle. In these cases it is suggested that the defect is anatomically or functionally closed during the systole.

This study would seem to indicate that the classical textbook description of interauricular septal defect is not entirely satisfactory. Such a diagnosis should not be made clinically without a thorough examination, including cardiac catheterization.

KELLY, Milwaukee.

MODERN TRENDS IN THE DIAGNOSIS AND TREATMENT OF CONGENITAL HEART DISEASE. M. M. EL-MEHAIRY, J. Roy. Egyptian M. A. **33**:370 (April) 1950.

Recent advances in diagnostic procedures and operative treatment are given for double aortic arch, patent ductus, coarctation of the aorta, and tetralogy of Fallot.

McGUIGAN, Evanston, Ill.

RETICULOENDOTHELIOSIS. H. WILLI and J. H. MÜLLER, Helvet. paediat. acta **5**:212 (June) 1950.

A 3 year old boy was given a diagnosis of reticuloendotheliosis of the Hand-Schüller-Christian type and was observed during eight years. In the course of the illness, and especially at the beginning, acute phases were observed, of which one had all the characteristics of the Letterer-Siwe disease. Intensive fractional x-ray therapy of the bones, combined with Bucky ray treatment of the skin, succeeds in tiding the child over the most acute phases of the illness. Histological and cytological studies reveal that the pathological process consists essentially in a proliferation of reticuloendothelial tissue and that accumulation of lipid material is entirely a secondary phenomenon.

FROM THE AUTHORS' SUMMARY.

DIAGNOSIS OF CONGENITAL PULMONARY STENOSIS WITH AURICULAR SEPTAL DEFECT. M. GROB, E. ROSSI, and M. BETTEX, Helvet. paediat. acta **5**:345 (July) 1950.

Basing their observations on five personal cases, the authors discuss the diagnosis and differential diagnosis of stenosis of the pulmonary artery with interauricular communication. Previously it was not possible to make a reliable diagnosis with the x-rays and clinical findings only, but the modern methods of investigation give enough clues to show the right diagnosis. The authors put the stress on angiocardiography (biphasic levogram), on the measure of the intracardial pressure, and on the amount of oxygen in the different heart cavities.

FROM THE AUTHORS' SUMMARY.

MEGALOBLASTIC ANEMIA IN INFANCY. Y. S. CHEN, D. E. PENG, C. CHAO, and J. SHEN, Chinese M. J. **67**:519 (Oct.) 1949.

The authors describe a case of megaloblastic anemia in a 13-mo.-old Chinese boy. The anemia responded promptly to liver and folic acid therapy. The pertinent literature is reviewed.

MACDONALD, Pittsburgh.

MECHANICALLY INDUCED DISTURBANCES IN THE HEART ACTION: OBSERVATIONS MADE ON HEART CATHETERIZATION OF ONE HUNDRED AND FORTY-TWO CHILDREN. BERNHARD LANDTMAN, Acta pædiat. **39**:1, 1950.

During heart catheterization of 142 children, of whom the majority had congenital heart disease, 160 cardiac disturbances were observed in 88 patients. None of the children revealed spontaneous arrhythmias before or after catheterization. The transient disturbances produced represented practically all known irregularities, including ectopic contractions, tachycardias, ectopic rhythms, auricular flutter, and irregularities due to disturbances in the stimulus conduction. No complications of clinical importance were observed.

The majority of the disturbances were registered when the tip of the catheter touched the infundibulum of the right ventricle and the pulmonary artery and the endocardial surface of the rest of the ventricle. Thus, the smaller ramifications of the specific conduction system seem to possess the highest ability of ectopic stimulus formation. Cardiac disturbances were also registered in some cases in which the tip of the catheter was inserted into the left side of the heart.

The disturbances were evaluated with regard to the electrocardiogram, the phonocardiogram, and the intracardiac pressure.

The results show that the mode of origin of cardiac disturbances is not specific, so far as the same mechanical excitation could give rise to different disturbances, both in the stimulus formation and in the stimulus conduction. Moreover, an excitation of one part of the specific conduction system could produce arrhythmias originating from other parts of the heart, even from those situated on the opposite side of the septum.

FROM THE AUTHOR'S SUMMARY.

UNIPOLAR LEAD ELECTROCARDIOGRAPHY IN CONGENITAL HEART DISEASE. CLAES-GÖRAN HERDENSTAM, Acta pædiat. **39**:33, 1950.

After a short report on unipolar-lead electrocardiography and its application in pediatric practice, the author describes the appearance of the Wilson unipolar electrocardiogram in

ventricular hypertrophy and auricular enlargement in children with congenital heart disease. The possibilities of diagnosing right or left ventricular hypertrophy by electrocardiographic means and thus of forming a valuable general conception of the nature of the cardiac malformation are demonstrated, with particular reference to cases of patent ductus arteriosus.

From the Author's Summary.

## Diseases of Nose, Throat, and Ear

Study of 30 Cases of Foreign Body in the Upper Air Passages and Upper Digestive Tract. Osvaldo Emhart, Rev. otorrhinolaring. **9**:3 (March) 1949.

Emhart presents 30 cases of foreign bodies in the airways and the upper digestive tract. The material covers a large variety of foreign bodies, 17 of which were lodged in the airways and 13 in either the hypopharynx or the esophagus. The age group of his patients ranged from 1 yr. 4 mo. to 12 yr. Most commonly the foreign bodies were present from one to three days. While some of the endoscopies were done with general anesthesia, most of the patients did not require any anesthetic. Three patients required tracheotomy. Three patients died. In one case of death the endoscopy was long and presented a difficult extraction of a watermelon seed in the bronchus; the second death was caused by heart failure and the third by secondary pulmonary complication. The author does not use any sedation prior to endoscopy. In complicated cases he advocates the use of both sulfonamides and penicillin. In conclusion, he advocates the establishment of bronchoesophagoscopic centers in which the personnel have adequate specialized training.

Persky, Philadelphia [Arch. Otolaryng.].

## Diseases of the Lung, Pleura, and Mediastinum

The "Wheezing Chest" in Children. Joseph Schwartzman and Cornelius H. Nau, Arch. Pediat. **67**:149 (April) 1950.

The authors publish a study of 151 cases of children admitted to the hospital with "wheezing chest." Of the patients, 88% were under 7 yr. of age and 58% were under 2 yr. of age. The sex incidence was roughly equal. Thirty-nine per cent of the cases were due to allergic causes, and this figure closely paralleled the number of family histories positive for allergic conditions. There were many diverse causes for the wheezing in the remaining 61% not due to allergy. In most of the patients under 2 yr. the tracheobronchial tree was involved directly. Tuberculosis was the etiological factor in eight cases. There were only two instances of foreign bodies in the bronchi. The authors were of the opinion that nasopharyngeal smears for eosinophiles were not as reliable as other writers had appeared to believe. The over-all mortality rate for this series of cases was 6%, a figure which should make one view with respect a child with a "wheezing chest."

Davis, Denver.

Indications for Pulmonary Resection in Infants and Children. John C. Jones, California Med. **72**:352 (May) 1950.

Improvements in anesthetic and surgical techniques and the availability of antibiotic drugs have made pulmonary resection a safe procedure, even for newborn and very ill infants, when it is necessary for the treatment of bronchiectasis, abscess of the lung, tumors, and congenital cysts, both infected and noninfected.

Of 34 infants and children upon whom lobectomy or pneumonectomy was done, all were cured of the disease which necessitated the operation. There were no deaths.

Pryor, Redwood City, Calif.

## Diseases of Gastrointestinal Tract, Liver, and Peritoneum

A Modified Test for Stool Trypsin: Its Use in Two Cases of Fibrocystic Disease of the Pancreas. Ralph Schwartz, Arch. Pediat. **67**:165 (April) 1950.

The author describes a simplified method for detecting the presence of trypsin in the stool. The required equipment consists of a test tube, a strip of exposed unfixed dental x-ray film, and

a suspension of the stool adjusted to a pH of approximately 8. Properly prepared, the test tube can be carried in the vest pocket, which serves as an incubator. In one group of 60 patients with unrelated diseases, and postnatal nursery patients on evaporated-milk diets, there was definite digestion of the x-ray film in every case on three separate determinations. In the second series there were two patients with cystic fibrosis of the pancreas. For these the stool tests for trypsin were indicative of no tryptic activity. Further investigation of both these patients confirmed the diagnosis of cystic fibrosis of the pancreas. This test is presented as a simple office procedure that should prove valuable in screening patients with steatorrheas.

DAVIS, Denver.

SURGICAL MANAGEMENT OF OMPHALOCELE. CHARLES HUGH MAGUIRE, Arch. Surg. **59**:484 (Sept.) 1949.

An omphalocele consists of a congenital defect in the anterior abdominal wall at the umbilicus, with little or no attachment or fusion of the normal fascia of the rectus muscles and extrusion of the peritoneal contents into a sac covered only by peritoneum and amniotic membrane. The embryologic and anatomic features involved in an omphalocele are discussed. The types of repair which may be necessary are described and illustrated by three case reports.

KAISER, Rochester, N. Y.

PROCTOLOGIC PROBLEMS OF INFANTS AND CHILDREN. JAMES B. GILLESPIE, Illinois M. J. **96**:371 (Dec.) 1949.

Gillespie points out that the most frequent proctologic diseases in childhood are ordinarily treated with success by medical measures. He discusses the diagnosis and treatment of anorectal strictures, anal fissures, proctitis, perianal dermatitis, anal fistula, prolapse of the rectum, megacolon, and dolichocolon. He also discusses the causes of passage of blood by rectum.

BARBOUR, Peoria, Ill.

CONGENITAL MALROTATION OF THE MIDGUT IN INFANTS. BROOX C. GARRETT and L. J. O'NEIL, New Orleans M. & S. J. **102**:539 (May) 1950.

Embryology, etiology, diagnostic points, and treatment of congenital malrotation of the intestine are briefly reviewed and four cases presented. Early diagnosis and treatment give a usually good prognosis.

MCGUIGAN, Evanston, Ill.

CONGENITAL MEGACOLON (HIRSCHSPRUNG'S DISEASE). HYMAN C. TOLMAS and BEDFORD H. BERRY, New Orleans M. & S. J. **103**:30 (July) 1950.

Two cases of congenital megacolon (Hirschsprung's disease) are reported with complete case reports. Both were apparently present in the first few weeks of life.

MCGUIGAN, Evanston, Ill.

CONGENITAL MEGACOLON: REPORT OF THREE CASES OF THE "OBSTRUCTIVE" TYPE TREATED BY RESECTION OF THE DILATED SEGMENT IN CONTRAST TO RESECTION OF THE DISTAL NARROWED SEGMENT. JOSEPH A. RITTER, HERBERT R. HAWTHORNE, and HARRY N. METZGER, Pediatrics **5**:791 (May) 1950.

Congenital megacolon of the obstructive type, currently attributed to agenesis of the intramural plexuses in the contiguous distal segment, is amenable to surgical treatment. Recently some authors have recommended resection of the distal neurogenically obstructed segment, while others have recommended resection of the proximal dilated segment. Although these procedures are contrastingly different, they both result in anatomic and functional improvement. Patients reported by the authors were treated by resection of the dilated proximal segment, and they demonstrate that the preferential choice of resection of the neurogenically obstructed segment may be on an equivocal physiologic basis.

FROM THE AUTHORS' SUMMARY.

HERPES SIMPLEX VIRUS NOT THE ETIOLOGIC AGENT OF RECURRENT STOMATITIS. KATHARINE DODD and ISAAC RUCHMAN, Pediatrics **5**:883 (May) 1950.

Over a period of years attempts by both Buddingh and Ruchman to isolate the virus of herpes simplex in cases of recurrent stomatitis have been unsuccessful. The present authors have recently studied the disease more intensively in 11 patients. Virus was isolated from the mouth of one patient in one attack but could not be found in subsequent attacks. One other patient had a rise in antibody titer during the period of observation, but all attempts to isolate the virus from her mouth were unsuccessful. In reported cases in which the virus has been recovered from the mouths of patients suffering from recurrent stomatitis or in which the titer of antibodies has arisen in the blood serum during the course of the disease, it seems probable that these were chance findings which bore no relation to the etiology of the disease.

FROM THE AUTHORS' SUMMARY.

STUDIES IN CELIAC DISEASE: FAT ABSORPTION. WILFRID SHELDON, and ANTOINETTE MACMAHON, Arch. Dis. Childhood **24**:249 (Dec.) 1949.

In children with celiac disease, a high content of dextrin in the diet (26 to 50% of the carbohydrate as dextrin) lowers the capacity to absorb fat much as does starch. In children with pancreatic fibrosis, the presence or absence of starch in the diet does not appear to affect the capacity to absorb fat. In this respect, pancreatic fibrosis is in contrast to celiac disease. Chylomicron counts in celiac disease indicate that defective absorption of particulate fat accounts, at least in part, for the failure to absorb fat adequately. Clinical improvement is accompanied by improvement in particulate fat absorption.

KELLY, Milwaukee.

A SKIN TEST FOR INFECTIOUS HEPATITIS. GERTRUDE HENLE, MILES DRAKE, WERNER HENLE, and JOSEPH STOKES JR., Proc. Soc. Exper. Biol. & Med. **74**:603 (April) 1950.

The Akiba strain of the infectious hepatitis virus was passed through chick embryo tissue culture 10 times, then transferred in 0.2-ml. amounts to the amniotic cavity of 8-day-old chick embryos. After incubation at 37 C. for seven days the whole contents of the eggs minus the albumin were emulsified in an equal amount of saline solution and passed amniotically to fresh embryos. Control materials were prepared under identical conditions. The material was stored at 4 C. There were 161 skin tests made, using 0.1 ml. in the right and left arm respectively of the infectious hepatitis and the control antigens. Tests were made on several groups, including (*a*) human volunteers who three months to two years previously had submitted to infection with the hepatitis virus as contained in stools and serum taken during the acute stage of the infectious hepatitis; (*b*) volunteers in another institution who had received five months to five years previously injections of a virus of the serum hepatitis; (*c*) 62 random subjects; (*d*) 9 young children, 2½ to 4 mo. of age, and (*e*) 10 patients with spontaneous hepatitis 12 days to six months after the onset of the illness. Positive skin reactions were characterized by an erythema with induration which as a rule exceeded 10 mm. in diameter and persisted after 24 hr., at times, up to one week. The control antigen caused no reactions in 149 of the cases studied. The optimal time for reading seems to fall between 24 and 36 hr. after administration. The skin reaction was positive strongly or at least weakly positive in all the volunteers exposed to the infectious hepatitis virus, and also in eight of nine of those in whom signs of infection had failed to develop because they were presumed to be immune at the time of exposure. The incidence of positive skin reactions was much lower in the patients who had volunteered previously to injection with the serum hepatitis virus. These patients had not revealed clinical or laboratory signs of infectious hepatitis. Only one of nine children without a history of recognized hepatitis gave positive results. This child apparently had suffered an illness six months previously which was compatible with hepatitis, although there had been no jaundice. The authors conclude that a skin-test antigen for infectious hepatitis has been prepared from amniotic fluid of chick embryos infected with the infectious hepatitis virus. It has apparently given specifically positive skin reactions in all the persons with past histories of spontaneous or induced infectious hepatitis. The incidence of positive reactions among patients with past serum hepatitis was no greater than that found in an adult population chosen at random.

HANSEN, Galveston, Texas.

FIBROCYSTIC DISEASE OF THE PANCREAS. FRANT WALT, South African M. J. **24**:294 (April 22) 1950.

The current theories regarding the etiology of fibrocystic disease are reviewed, and diagnostic points are stressed. The importance of early recognition and intensive use of antibiotics and sulfonamides are emphasized.

McGUIGAN, Evanston, Ill.

MOTILITY OF THE STOMACH IN INFANTS. W. KELLER, Ann. pædiat. **174**:273 (May) 1950.

The stomach empties in the individual infant at a constant rate. A method has been evolved to ascertain the speed at which the stomach empties, in cubic centimeters an hour.

Comparative estimates in 60 premature and full-term babies of weights varying between 800 and 7,700 gm. show that the stomach emptying speed and the body surface of the babies is strictly proportionate: 1m.$^2$ of the body surface corresponds to 214 cc. of breast milk an hour.

Hunger accelerates the emptying, which tends to become very precipitous after prolonged hunger periods.

Experiments carried out on the surviving and isolated human stomach show that it works at a constant rate, independent from the state of filling. The surface of the stomach is proportionate to the body surface.

FROM THE AUTHOR'S SUMMARY.

LAX PERITONEAL LIGAMENTS. A. GRASSI, Lattante **21**:84 (Feb.) 1950.

A boy with abdominal pain and diarrhea was found to have a megadolichocolon and abnormally relaxed peritoneal ligaments, especially those supporting the liver and the large bowel.

HIGGINS, Boston.

ALIMENTARY TOXICOSIS—OCCULT MASTOIDITIS. H. OPITZ, Kinderärztl. Praxis **16**:208 (July-Aug.) 1948.

The case of a 4-mo.-old girl with the following symptoms: anorexia, vomiting, loss of weight, diarrhea, and fever, is described. The physical findings showed dullness of both eardrums; paracentesis-produced serous fluid and bilateral antrotomy with the patient under local anesthesia showed necrotic foci bilaterally with thick creamy pus, culturing hemolytic streptococci. After surgery the patient improved at once, except for the persistence of fever for several days, during which the patient received 10,000 units of penicillin every two hours for four days. The author emphasizes the difficulty in diagnosis and the frequent relation of mastoiditis with nutritional disturbance and considers that the treatment of occult mastoiditis by surgery may in the future be replaced by early penicillin and sulfonamide therapy.

GLASER, Chicago.

INVOLVEMENT OF THE LIVER SEROSA IN HEPATITIS. H. ZIESCHE, Kinderärztl. Praxis **16**:330 (Nov.-Dec.) 1948.

Systematic follow-up examination in cases of hepatitis in children and young adults has attracted the author's attention to the complaints of pains by these patients three to 12 mo. after a case of acute hepatitis. Liver function tests gave negative results. The pains were of a burning, stinging, or pulling character, were usually in the right upper quadrant, and were aggravated by physical activity leading to shaking of the body or by prolonged standing. Enlargement of the liver at that time was either absent or so minimal that the author did not believe that it could be the cause for the pains; rather, he attributed the pains to a direct involvement of the serosa covering the liver, which led to the formation of adhesions which might later on dissolve again. At times a friction rub could be heard or felt over the liver area.

The author recommends heat therapy, especially short-wave diathermy, as most effective. Rest and avoidance of shaking motions, prolonged standing, and constricting clothes are also important.

GLASER, Chicago.

FATAL GASTROENTEROCOLITIS OF UNUSUAL BACTERIAL GENESIS IN A CHILD. W. ZISCHKA, Wien. klin. Wchnschr. **62**:409 (June 9) 1950.

Zischka reports the case of a 2½ year old boy who was taken ill with vomiting and then had severe diarrhea, with fever and somnolence. Within three days the child died. From the

small intestine a Staphylococcus was isolated. An eight-day-old broth culture was filtered so that the filtrate was sterile. The presence of an enterotoxin was demonstrated by means of the Dolman, or cat, test. The boiled filtrate was injected intraperitoneally in a young cat, which reacted with vomiting after about 1 hour. Very few cases of Staphylococcus food intoxication with a fatal outcome have been reported.

AMBERG, Rochester, Minn.

CONGENITAL STENOSIS OF JEJUNUM. W. Y. WU and L. C. CHU, Chinese M. J. **67**:527 (Oct.) 1949.

Wu and Chu report a case of congenital stenosis of the jejunum, the first in the Chinese literature. The intestine was not resected, but a side-to-side anastomosis was made. The patient recovered.

MACDONALD, Pittsburgh.

SEVERE HYPOPROTEINEMIA, PROBABLY CAUSED BY HEPATIC DAMAGE. BENGT J. JONSSON and VIVEKA LAGERCRANTZ, Acta pædiat. **39**:165, 1950.

The authors describe a case of hypoproteinemia with severe edema, probably as the result of disturbed protein syntheses. Histologic examination showed interstitial fibrosis of the liver.

FROM THE AUTHORS' SUMMARY.

## Nervous Diseases

BACTERIAL MENINGITIS: RESULTS OF TREATMENT IN SEVENTEEN CASES WITH A NEW SULFONAMIDE (GANTRISIN®). P. S. RHOADS, F. A. SVEC, and J. H. ROHR, Arch. Int. Med. **85**: 259 (Feb.) 1950.

Ten patients with meningococcic meningitis were treated with gantrisin,® a new sulfonamide with the formula 3,4-dimethyl-5-sulfanilamide-isoxazole, which was used as the sole bacteriostatic agent. All recovered without complications resulting from the disease or the treatment.

Two patients with meningococcic meningitis, three with pneumococcic meningitis, and two with Hemophilus influenzae meningitis were treated with gantrisin® and one of the antibiotics. One of these patients, shown at autopsy to have pneumococcic endocarditis, died. All the others recovered.

Gantrisin® was administered orally, intramuscularly, and intravenously, with no untoward effects. Several patients who had albuminuria and microscopic hematuria at the start of treatment with gantrisin® were given the drug in full doses without adjuvant alkali therapy; the conditions cleared up under treatment.

ALPERS, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

ASTROCYTOMAS OF THE CEREBELLUM. ROBERT F. MABON, HENDRIK J. SVIEN, ALFRED W. ADSON, and JAMES W. KERNOHAN, Arch. Neurol. & Psychiat. **64**:74 (July) 1950.

One hundred and thirty-one cerebellar astrocytomas occurring over a period of 30 yr. are reviewed. Eighty-three per cent of these were Grade 1. There were twice as many cystic as solid tumors, with no difference in prognosis.

McGUIGAN, Evanston, Ill.

HUMAN FETAL BRAIN CELLS IN TISSUE CULTURES: THEIR IDENTIFICATION AND MOTILITY. MARY JANE HOGUE, J. Exper. Zool. **106**:85 (Oct.) 1947.

Hogue grew explants from the brains of human fetuses ranging from 27 to 185 mm. (crown-rump length) in special mediums—in hanging-drop or in roller-tube cultures. The oldest cultures were flourishing after 143 days, at which time the incubator broke down.

There is early differentiation of many fetal brain cells into their characteristic adult forms: oligodendrogliocytes, macrophages, granule cells, cells of Golgi type II, Purkinje cells, and giant nerve cells. Oligodendrogliocytes are the first cells to migrate from cerebellar explants, and these are followed by macrophages, then granule cells and later by Golgi type II cells, Purkinje cells, giant nerve cells, and many other types of nerve cells. The branched processes of the brain cells are constantly changing their shape and size, and they form a neuropil around the explanted tissues. Photomicrographs taken at intervals show that human fetal nerve cells migrate slowly and have a definite polarity. Purkinje cells migrate with two large dendrites

directed anteriorly and an axon following posteriorly. In the Purkinje cells, in the giant nerve cells, and in a few other cells granules were distinctly seen. In many nerve cells a nucleus with one or more nuclei was visible. Some nerve cells had two or three nuclei, or even a bilobed nucleus.

The definite relation to the nerve cells which the oligodendroglia cells maintain may be symbiotic. Manipulation of the tissue cultures produces a quicker response in the nerve cells (contraction) than in fibroblasts, epithelial cells, or muscle cells. Nerve cells do not often liquefy coagulated chicken plasma, even in old cultures.

Such a study of living brain cells by the tissue-culture method shows the enormous variety of forms which these cells can assume and their manner of association with each other.

The discussion section includes a review of the literature dealing with mammalian brain cells in tissue cultures. REID, New Brunswick, N. J. [ARCH. NEUROL. & PSYCHIAT.].

MASSIVE SPONTANEOUS HEMORRHAGE IN GLIOMAS: A REPORT OF SEVEN VERIFIED CASES. L. O. J. MANGANIELLO, J. Nerv. & Ment. Dis. **110**:277 (Oct.) 1949.

Manganiello reports the clinical and pathological features of seven cases of massive spontaneous hemorrhage in gliomas occurring in a series of 183 gliomas. He stresses the clinical importance of focal, progressive neurological signs and symptoms antedating the symptoms of hemorrhage as a point of differential diagnosis when primary vascular hemorrhage is considered. Of the 183 gliomas, 3.8% produced this syndrome of massive spontaneous hemorrhage, and spongioblastoma multiforme comprised 43% of the tumors with massive hemorrhage. The author subscribes to the view that intracerebral hemorrhage is preceded by softening of the brain tissue, which thereby deprives a vessel wall of support at a focal point.

FARMER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

THE MOTOR CORTEX IN AMYOTONIA CONGENITA. WALTER FREEMAN, J. Neuropath. & Exper. Neurol. **5**:207 (July) 1946.

Freeman reports the case of a girl aged about 4 mo. who from the time of birth had never moved her legs and who showed only slight movements of the arms. The cry was weak and husky. Nursing was difficult, and the child had to be stimulated constantly to suck; exhaustion developed quickly on effort. The child remained in the hospital for about three months and made little or no progress. At home, a good state of nutrition could not be maintained, and she was hospitalized because of increased temperature, dyspnea, and cyanosis. Examination showed a deep funnel deformity of the chest with retraction being purely diaphragmatic. The lower limbs were flaccid, and the upper ones, almost so, although there was a little tone in the biceps and the fingers were contracted in flexion. No tendon reflexes were obtained. The corners of the mouth were turned downward; they showed moderate retraction during crying, which was almost soundless. Sucking was weak and soon exhausted. Mucus had to be aspirated from the pharynx and larynx, since the child could apparently neither swallow nor cough it up. Even in a respirator with oxygen the child grew weaker and died within 24 hr.

Necropsy was performed, and Freeman observed that the pathologic alterations in the central convolutions in three other cases, in which there was complete necropsy, were identical with those in the present case. In two other cases which he had studied the material available to him was insufficient. Freeman's studies indicate that the cortical changes in amyotonia congenita are definite, but they have attracted little notice heretofore. He states, "While the deficiency of ganglion cells was spectacular only in respect to the giant multipolar cells of Betz, it was still fairly obvious in layer III and even in layer I. The cortex was also immature in the arrangement of cells, a tendency to columnar orientation being observed. In the matter of individual configuration, the "Betz" cells in amyotonia were relatively undeveloped. They showed a pyramidal rather than polygonal shape, with prominent vesicular nuclei but little chromatin material, few processes and no definite neurofibrils. No degenerated cells were seen; they were rather of the immature type. The feltwork of processes in the vicinity of these cells was more delicate than that seen in the control case.

"Comparison of the postcentral convolutions of the amyotonia case with the normal also showed pronounced immaturity, the cells being fewer in number, especially in layers III, IV and

VI, and tending to be arranged in columns. Layers I, II and V were less strikingly altered. No other deficiencies were noted in the central nervous system and there was no deposit of fat to suggest parenchymatous breakdown. . . .

"This may prove to be an important point in differentiating this disease pathologically from infantile spinal muscular atrophy."

GUTTMAN, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

CURARE IN SPASTIC PARAPLEGIA. IRVING S. COOPER and THOMAS I. HOEN, J. Neurosurg. **5**:464 (Sept.) 1948.

Cooper and Hoen report the effects of curare on eight paraplegic patients. All had severe flexor spasticity of the lower extremities. The patients were given purified chondodendion tomentosum (intocostrin®) in doses sufficient to produce side effects that made it necessary to discontinue the drug. None of the patients demonstrated a decrease in the spasticity of the affected muscles.

Cystometrograms were obtained daily during the administration of the curare. The hypertonicity of the bladder was not affected.

TOZER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

SURGICAL RELIEF OF SPASTICITY IN PARAPLEGIC PATIENTS: II. PERIPHERAL NERVE SECTION, POSTERIOR RHIZOTOMY, AND OTHER PROCEDURES. L. W. FREEMAN and R. F. HEIMBURGER, J. Neurosurg. **5**:556 (Nov.) 1948.

Ambulation is of prime importance in the rehabilitation of paraplegic patients. One of the most frequently encountered difficulties hindering it is the uncontrolled reflex spasms of certain muscle groups in the limbs and abdomen. Freeman and Heimburger report their methods of treating such spasms.

For relief of adductor spasms of the lower extremities, they use section of the obturator nerve at the obturator canal. For reduction of contracture deformities in which the Achilles tendon had become shortened, section of the sciatic nerve with immediate resuturing gives enough time before reinnervation takes place for correction of the deformity. Section of the nerve was done in the popliteal space. Other peripheral nerves may be sectioned for relief of spasm in the appropriate muscle group. Rhizotomy of the posterior nerve roots has not been satisfactory in the treatment of reflex spasms in paraplegic patients. Injection of 95% alcohol directly into the spinal cord for the relief of massive spasms has been used, especially if decubitus makes anterior rhizotomy impractical. Subarachnoid injection of alcohol is done only as a temporary measure. It has an effect similar to anterior rhizotomy, but of shorter duration. Continuous spinal or caudal anesthesia exerts no permanent effect on spasticity. Sympathectomy has no appreciable effect in lessening the spasticity. Only in cases of gross neglect are destructive orthopedic procedures to the joints justified.

TOZER, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

PLATYBASIA. CLARA MAYERSZKY, J. Neurol., Neurosurg. & Psychiat. **12**:61 (Feb.) 1949.

Platybasia may be classified into primary basilar impression, which results from a defect in craniovertebral development, and secondary basilar impression, which results from diseases causing softening of bone, such as osteitis deformans, rickets, and osteomalacia. The diagnosis can be made by roentgenogram, which in the lateral view shows an increase in the basal angle. Neurologic signs include paraplegia, quadriplegia, ataxia, nystagmus, dysphagia, dyspnea, and dysarthria. The treatment is surgical. The author reports a case of platybasia secondary to rickets in which the condition responded to operative intervention consisting of upper cervical laminectomy and suboccipital decompression.

N. MALAMUD, San Francisco [ARCH. NEUROL. & PSYCHIAT.].

ACUTE GENERAL EDEMA OF THE BRAIN IN CHILDREN WITH HEAD INJURIES. WILFRED PICKLES, New England J. Med. **242**:607 (April 20) 1950.

This paper continues the author's observations concerning head injuries in children delineated in the *New England Journal of Medicine* (**240**:92 [Jan. 20] 1949). In this previous paper he

makes the suggestion that acute focal edema of the brain following injury to the head may bring about a pathologic state that mimics middle meningeal artery hemorrhage. This visible clinical edema of the motor cortex was demonstrated in two cases at operation.

In the present paper eight cases are described in which head trauma was followed in about 30 min. by unconsciousness and coma. These children were admitted appearing near death from medullary compression. They usually had no reflex responses or spontaneous movement of the extremities. Shock was not present, and the blood pressure was not depressed. Before contemplated surgery was accomplished, however, improvement was noted, and recovery ensued in about two hours from the onset of the alarming symptoms.

Because the author does not believe in performing a lumbar puncture when acute shock is present or when intracranial bleeding is suspected, data relating to the spinal fluid in the acute phase of this symptom complex are not available. Taps done when the acute phase had passed gave negative results except in one instance.

The author suggests that acute general edema of the brain with capillary anemia is responsible for the picture described above, and he supplements his belief with excerpts from past neurological writings of note.

WHEELOCK, Denver.

TREATMENT OF LEAD ENCEPHALOPATHY WITH BAL (2,3-DIMERCAPTOPROPANOL). JULIUS M. ENNIS and HAROLD E. HARRISON, Pediatrics **5**:853 (May) 1950.

In this study 16 patients with encephalopathy due to lead were treated with dimercaprol (BAL) for periods of 10 days. Of these, nine were admitted in coma or convulsions. The mortality in this group was 22%, compared with a mortality in the control group of 66%. Conclusions from the study were that dimercaprol was effective in lowering the mortality and reducing the severity of residual symptoms in children with severe lead encephalopathy. No conclusive effects of therapy could be demonstrated in subacute mild cases. The toxic effects of dimercaprol were limited to nausea and vomiting which were not severe enough to contraindicate continuation of treatment. There was no evidence of exacerbation of symptoms in mild cases of lead poisoning treated with dimercaprol. Dimercaprol administration increased the urinary excretion of lead for a limited time, and this effect could be repeated in the same patient after an interval. The concentration of lead in the blood fell spontaneously after removal of children with lead poisoning from their source of exposure by admission to the hospital. The rate of decrease in blood lead was not influenced by dimercaprol administration.

FROM THE AUTHORS' SUMMARY.

RECOVERY WITHOUT INTRATHECAL THERAPY OF A FOUR DAY OLD INFANT WITH INFLUENZAL MENINGITIS. JACK SEGAL, and FONTAINE S. HILL, Pediatrics **6**:33 (July) 1950.

A case of Hemophilus influenzae meningitis in a 4-day-old infant is reported in which recovery was obtained without intrathecal medication. Treatment consisted of parenteral administration of streptomycin, sulfadiazine sodium and penicillin.

FROM THE AUTHORS' SUMMARY.

ULTRAVIRAL MENINGITIS AND ENCEPHALOMYELITIS. ETIENNE KORNYEY, Encéphale **38**:266, 1949.

Kornyey has been engaged in the task of delimiting the diseases of indubitable virus etiology and the diseases in which, until very recently, such an origin has been purely hypothetical. In the latter group he claims to have found some diseases for which he could demonstrate a microbial agent. For others an allergic cause has been favored by a large number of authorities. He discusses diseases of the leptomeninges, polioencephalomyelitis, and some diseases recently regarded by Pette as panencephalitis.

Among the benign meningitides, he finds a form which appears to be characterized by persistence for about four weeks of the pleocytosis, even in cases in which the clinical symptoms existed only for several days. This type of evolution appears to be characteristic of meningitis due to an ultravirus; at least it represents one of its typical forms of evolution. By this sort of prolonged course the benign meningitis is differentiated from the meningitic forms of poliomyelitis,

in which the pleocytosis usually lasts only four to eight days. In the diagnostic use of the information furnished by the cerebrospinal fluid in both benign meningitis and poliomyelitis, one must take into account the stage of the disease during which the fluid was obtained. The author reserves his opinion as to whether there also exist atypical cases of viral benign meningitis complicated by parenchymal lesions. Nevertheless, it appears certain that papilloretinitis, even of a severe degree, may complicate such disease.

There is need of a revision of the concept of neurotrophy with regard to the viral diseases of the parenchymal nerve tissue. The diseases of this group constitute a series, beginning with poliomyelitis, characterized by an elective gangliocellular destruction, and ending with certain encephalomyelitides, in which there appears to be no essential separation of the histologic process in the white and in the gray matter. Abortive poliomyelitis should not include those cases in which the disease is not accompanied with pleocytosis. In the initial stages of poliomyelitis, the prognostic value of the relation between polymorphonuclear cells and lymphocytes in the cerebrospinal fluid is limited, but not entirely negligible if one takes into account the stage of clinical evolution. In view of the regular partition of the histologic process in the disease, one should exercise a prudent reserve concerning atypical forms, particularly when the symptoms of a cerebral lesion permit the exclusion of poliomyelitis.

ZINKIN, New York [ARCH. NEUROL. & PSYCHIAT.].

TETANIC SYNDROME WITHOUT CHANGE IN BLOOD CHEMISTRY APPEARING IN JUVENILE DEMENTIA PARALYTICA. L. VAN BOGAERT, Monatsschr. Psychiat. u. Neurol. **118**:30 (July) 1949.

Van Bogaert reports the case of a boy aged 13 who was stricken with juvenile dementia paralytica and whose father was hospitalized with the adult form of the disease. Clinically, he presented pupillary changes, cerebellar signs, speech disturbance of a dysarthric nature, and visual diminution, culminating in blindness due to bilateral optic nerve atrophy. He gradually became bedridden, and quadriplegia in flexion developed. He was also subject to epileptic seizures. During a three-year period of progression of his illness, opisthotonos and carpal spasm were observed, the least touch precipitating generalized muscular hypertonia. The cramps produced by the manipulation of his extremities were painful, and his face assumed a sardonic smile. The Chvostek and Trousseau signs were positive on both sides. The calcium and phosphorus levels of the blood were not elevated. The Wassermann reactions of the blood and the spinal fluid were positive, with an increase in the cells and protein of the spinal fluid. Deglutition became difficult, so that the patient had to be tube fed. During the terminal period there was marked contracture of the extremities, with exaggeration to tactile stimulation.

Pathologically, there was no evidence of parathyroid disease. The brain showed evidence of meningeal thickening and generalized atrophy. The cortex showed extensive cellular changes of the Lissauer type. Histologically, of interest was the presence of pseudocalcific deposits both in the parenchyma and along the vessels, particularly of the putamen, thalamus, and pallidum. These lesions resembled the "idiopathic perivascular calcification" of Fahr. Strangely, in the areas showing this alteration there was no evidence of the spongy state or of serous inhibition of the tissues.

PISETSKY, New York [ARCH. NEUROL. & PSYCHIAT.].

PHOTIC STIMULATION AS AN AID IN ELECTROENCEPHALOGRAPHY: A REPORT OF THREE CASES. KARL-AXEL MELIN, Acta pædiat. **39**:148, 1950.

Three cases of epilepsy are reported, in all of which the patients were examined by means of electroencephalography and photic stimulation. This activation method increases the accuracy of the electroencephalographic examination, and 4 to 8% of the epileptics react positively. During the electroencephalographic examinations the eyes are illuminated from a stroboscope with a lamp emitting very short, brilliant light impulses of different frequencies. Many normal subjects respond to the intermittent light impulses at certain frequencies with synchronous brain rhythms. In some epileptics, however, photic stimulation of this type will either evoke seizure discharges in the electroencephalogram at certain light frequencies or induce clinical seizures. This was the case in the three subjects described.

FROM THE AUTHOR'S SUMMARY.

## Psychology and Psychiatry

DEMENTIA WITH PALILALIA IN AN ADOLESCENT: CORTICAL AND SUBCORTICAL LESIONS DUE TO DIFFUSE CEREBRAL ENDARTERITIS. L. FROMENTY, Encéphale **38**:49, 1949.

Fromenty reports the case of a white girl aged 20 with no familial, hereditary, or personal disease of any significance. Until the age of 15 she had been considered healthy, robust, and normal. Her disease began insidiously with an increasingly poor scholastic effort, followed within two years by dementia. She remained at home, lazy, inert, dreamy, and indifferent, with occasional long fugues, during which she wandered about. On examination in 1943, she showed puerile, agitated behavior, was slovenly in dress and comportment, had pronounced disturbances of association and thinking (Bleulerian type), and was inattentive, with intermittent palilalia. In the hospital she exhibited mental confusion and was violently agitated, refusing all food. Moderate spiking fever was attributed to pulmonary tuberculosis of the right lung, which cleared before her death. The course during her last three months of life was marked by increasing cachexia, stupor, mutism, delirious episodes, and, always, prominent palilalia. She died about 18 mo. after she was first studied, of perforation of the intestine. The author especially notes that the palilalia was intense and that it paralleled her mental confusion and agitation. She also exhibited logorrhea, with no formed phrases or sentences; there was no word salad. The logorrhea seemed explosive and compulsive. Neurologic examination was essentially noncontributory.

The entire brain was sent to Prof. O. Vogt's laboratory, in Neustadt, Germany, where it was sectioned and studied. It weighed 1,130 gm. There were two types of lesions, the vascular and the parenchymatous. The vascular lesions were of peculiar type and diffuse, with extensive changes in arteries and arterioles of the gray matter of the cortex and the central nuclei. There was conspicuous hyperplasia of the vascular endothelium with many occluded vessels. There was some formation of new vessels. The lesion was an endarteritis with a tendency to obliteration, but nowhere was there any inflammatory lesion, cellular infiltration, either in the wall or in the perivascular spaces, thrombi, emboli, or softening.

Lesions of the second type involved the nerve tissue itself. The cortical cells showed regression, with disappearance of cells in some areas. The tigroid material had disappeared; the cells were contracted and showed fatty vacuolation. The nuclei of the cells showed hyperchromatosis, progressing to pyknosis. The cellular lesions were not similar to those observed with schizophrenia. The disappearance of nerve cells was prominent in the left third frontal gyrus (Broca's area), as well as in the insula. Other frontal and prefrontal gyri were intact. There were less prominent lesions in the temporal lobe; these were localized to the third cortical layer (second sublayer of the third layer of cortex), involving the layer of medium-sized pyramidal cells. There was no evidence of neuroglial reaction. The striate body showed vacuolar degeneration with the cell nuclei in fair state. The lesions were more pronounced in the putamen than in the caudate nucleus; but the maximal disturbance was in the globus pallidus, where it was greater than in the cortex itself. There was conspicuous disappearance of cells without neuroglial reaction. Tuberculosis was considered as the cause of death.

The course of the disease clinically suggested schizophrenia, but at no time in the five years had there been any catatonic or paranoid features. The histologic study of the lesions were not those of dementia precox. Buerger's disease (thromboangiitis obliterans), cerebral type, was considered but was ruled out by the pathologic picture. The origin remains a mystery. The author makes a plea for more complete and systematic anatomoclinical studies in psychiatric cases.

ZINKIN, Fort Worth, Texas [ARCH. NEUROL. & PSYCHIAT.].

## Diseases of Genitourinary Tract

HYPERCALCEMIA, NEPHROPATHY AND ENCEPHALOPATHY FOLLOWING IMMOBILIZATION: CASE REPORT. KATHARINE DODD, HARRY GRAUBARTH, and S. RAPOPORT, Pediatrics **6**:124 (July) 1950.

The case of an active 12-year-old boy who was suddenly immobilized after fracture of a femur is presented. The prolonged immobilization led to hypercalcemia and renal damage, with hypertensive encephalopathy and osteoporosis. After the withdrawal of calcium from the diet,

intravenous administration of fluids and increase in the child's activity, the serum calcium gradually returned to a normal level and signs of hypertensive encephalopathy and of renal damage disappeared. The pathogenesis of acute osteoporosis following sudden immobilization is briefly discussed.

FROM THE AUTHORS' SUMMARY.

SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS IN INFANCY AND CHILDHOOD. A. COLIN P. CAMPBELL and J. L. HENDERSON, Arch. Dis. Childhood **24**:269 (Dec.) 1949.

The clinical and pathological features of symmetrical renal cortical necrosis in childhood have been reviewed. Four personal cases are described, including two cases in infants, the first to be recorded in this age period. Nine other cases occurring in children under 15 have been found in the literature, and these have been reviewed.

The clinical features of the disease in childhood are similar to those of cases in adult life. Anuric or oliguric renal failure is the predominant feature. But the occurrence of vascular disturbances in other parts of the splanchnic vascular bed is emphasized, notably in the bowel; diarrhea, with or without passage of blood, is a frequent symptom. The renal lesion is regarded as the predominant feature of a splanchnic vasospastic syndrome.

KELLY, Milwaukee.

ON THE ABILITY OF ENURETIC CHILDREN TO HOLD URINE. NIILO HALLMAN, Acta pædiat. **39**:87, 1950.

The functional bladder capacity has been tested in 63 enuretics (45 boys and 18 girls) by endeavoring to get the children to hold their urine as long as possible. Among the cases there were no organic diseases, infections of the urinary passages, cases of debility, or patients suffering from endocrine diseases. Compared with the control material (81 boys and 48 girls), the capacity of the bladder was generally lower in the enuretics, apart from a few exceptions.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF HYALURONIDASE ON HYPODERMOCLYSIS IN INFANTS. NIILO HALLMAN, EINO KULONEN, and OLOF FORSANDER, Acta pædiat. **39**:94, 1950.

The authors studied the effect of testicular and bacterial hyaluronidase on the resorption of fluids introduced subcutaneously, as well as their influence on the excretion of urine. The bacterial preparation, which is much cheaper, was found to be as efficacious as and had fewer untoward effects than the impure testicular preparation. The rate of urinary excretion rose considerably.

FROM THE AUTHORS' SUMMARY.

## Diseases of Ductless Glands; Endocrinology

ROENTGENOLOGIC FINDINGS IN MYASTHENIA GRAVIS ASSOCIATED WITH THYMIC TUMOR. C. ALLEN GOOD, Am. J. Roentgenol. **57**:305 (March) 1947.

Good reviewed 100 consecutive cases of myasthenia gravis.

In each there were a posteroanterior roentgenogram of the chest and either a fluoroscopic examination or a lateral roentgenogram of the chest or both.

In 17 cases there was roentgenologic evidence of a mass in the anterior mediastinum. Of these, surgical exploration was made in 11 and postmortem examination in three others. In all 14 cases there was a tumor of the anterior mediastinum, in 13 of which it proved histologically to be of thymic origin. In the one case histologic findings were indeterminate.

Roentgenologically two types of tumor may exist. The first type produces a well-defined shadow, which will be disclosed by any type of roentgenographic examination of the thorax. The other type of tumor is shaped like a plaque and is closely attached to the anterior pericardium and great vessels. The only evidence of this tumor may be a shadow, best described as a "fullness" in the clear space of the anterior mediastinum. It may pulsate because of proximity to the heart.

Most of the tumors in the present series were in the upper mediastinum, overlying the aortic arch and the base of the heart. None were above the suprasternal notch. In three cases the tumor was lower, being at the level of the ninth thoracic vertebra.

Calcification of the tumor was found roentgenologically in two cases.

TEPLICK, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

THE RELATIONSHIP OF THE MOUSE ADRENAL CORTEX TO THE PITUITARY. I. CHESTER JONES, Endocrinology **45**:514 (Nov.) 1949.

The traditional zoning of the mammalian adrenal cortex on histological grounds may well be paralleled by divisions of physiological function. In the mouse, at least, it is clear that three zones, the zona glomerulosa, the zona fasciculata, and the X-zone, have different relation with the pituitary gland.

JACOBSEN, Buffalo.

ACCELERATED GROWTH WITH SEXUAL PRECOCITY IN FEMALE MONKEYS RECEIVING TESTOSTERONE PROPIONATE. G. VAN WAGENEN, Endocrinology **45**:544 (Nov.) 1949.

It has been possible to double the growth rate and reduce by half the age of the young female monkey at the time of menarche (first menstruation). The androgen, testosterone propionate, was the agent used.

JACOBSEN, Buffalo.

FUNCTIONAL INTRASPLENIC OVARIAN TRANSPLANTS IN MONKEYS. G. VAN WAGENEN and W. U. GARDNER, Endocrinology **46**:265 (March) 1950.

Although hepatic tissue of rodents undoubtedly inactivates estrogens, the evidence presented here indicates that the monkey's liver will not inactivate the estrogen produced by one-half of one ovary.

In this particular, the primate is unlike the rodent, whose physiological responses form the basis for so much of the present thinking.

JACOBSEN, Buffalo.

DIABETOGENIC EFFECT OF PURIFIED GROWTH HORMONE. JAMES CAMPBELL, L. W. F. DAVIDSON, W. D. SNAIR, and H. P. LEI, Endocrinology **46**:273 (March) 1950.

The purpose of this investigation was to determine which components of the anterior pituitary gland possess diabetogenic activity.

Evidence is presented which indicates that for the dog the growth hormone is the important diabetogenic substance of bovine anterior pituitary glands, with respect both to activity and to the total amount present in the gland.

Corticotrophin (ACTH) elicits signs of diabetes (hyperglycemia and glycosuria) which are much less intense than those produced by the growth hormone.

JACOBSEN, Buffalo.

"SCOTTIE"—TWELVE YEARS DIABETIC. FREDERICK M. ALLEN and JAMES R. LISA, Endocrinology **46**:282 (March) 1950.

A dog with severe diabetes after partial pancreatectomy was able to live for 12 yr. under control of the sugar with insulin, without organic or vascular pathologic change. The continuous limitation of calories and body weight is suggested as possibly prolonging both life and vigor, in accord with demonstrations in other species. Some interrelations of human and canine diabetes are discussed.

JACOBSEN, Buffalo.

THE MECHANISM OF ESTROGEN INHIBITION OF COMB GROWTH IN THE COCKEREL, WITH HISTOLOGIC OBSERVATIONS. NORMAN F. BOAS and ARTHUR W. LUDWIG, Endocrinology **46**:299 (March) 1950.

The administration of estradiol to immature male chicks prevents the normal growth and development of the comb. There is evidence that the estrogenic inhibition of comb growth is dependent on the suppression of gonadotropin secretion in the adenohypophysis.

JACOBSEN, Buffalo.

RENAL FACTORS IN THE ADRENAL CORTICAL CONTROL OF WATER METABOLISM. W. R. BOSS, JAMES H. BIRNIE, and ROBERT GAUNT, Endocrinology **46**:307 (March) 1950.

It is now well established (*a*) that the diuretic response to water is subnormal or lacking in either animals or humans with adrenal insufficiency; (*b*) that this deficiency is peculiarly refractory to replacement therapy; (*c*) that there is a susceptibility to water intoxication after adrenal-

ectomy, because of extrarenal as well as renal abnormalities, and (*d*) that water diuresis is stimulated in normal animals by administration of hormones of the adrenal cortex.

The present study is an attempt to determine the importance of variations in glomerular filtration and tubular reabsorption of water (*a*) in adrenal-deficient animals receiving diuretic or intoxicating doses of water, (*b*) in adrenalectomized animals treated with adrenal steroids, and (*c*) in intact animals after overdosage with adrenal steroids.

Results of the experiments indicate that, while maintenance of a normal filtration rate is obviously a function of importance, the primary action of cortical hormones on water excretion is to inhibit the tubular reabsorption of water.

JACOBSEN, Buffalo.

THE INABILITY OF EPINEPHRINE OR ADRENOCORTICOTROPIC HORMONE TO DEPLETE THE ASCORBIC ACID CONTENT OF THE CHICK ADRENAL. JOSEPH W. JAILER and NORMAN F. BOAS, Endocrinology **46**:314 (March) 1950.

It has been demonstrated that the administration of corticotrophin (ACTH) results in an almost immediate fall in the cholesterol and ascorbic acid content of the rat and guinea pig adrenal gland.

The experiments here reported seem to indicate that, contrary to experience with the rat and guinea pig, the release of corticosteroids from the chick adrenal is not dependent upon a fall in the adrenal ascorbic acid.

JACOBSEN, Buffalo.

THE ANTIDIABETIC ACTION OF INSULIN ON NITROGEN METABOLISM. I. L. CHAIKOFF and L. L. FORKER, Endocrinology **46**:319 (March) 1950.

The antidiabetic action of insulin has been studied in depancreatized dogs. When the quantity of insulin injected fell below a certain level, a negative nitrogen balance ensued. Nitrogen balance was approximately linearly related to the amount of insulin injected under the particular conditions of these experiments.

JACOBSEN, Buffalo.

SUCCINIC DEHYDROGENASE AND ANAEROBIC GLYCOLYSIS IN LIVERS OF DIABETIC RATS. ELVA G. SHIPLEY, ROLAND K. MEYER, J. H. COPENHAVER JR., and W. H. MCSHAN, Endocrinology **46**:334 (March) 1950.

In the diabetic animal carbohydrate metabolism is markedly altered, with the result that protein and fat storage are decreased and a large part of the glucose is lost in the urine, with concomitant loss of depot fat, loss of nitrogen, and failure of growth. In view of the modern concept that enzymes play a fundamental role in cellular metabolism, one can postulate that insulin is interacting with, or in some way affecting, the action of enzymes.

The experiments here reported indicate that in diabetic lactating rats the succinic dehydrogenase activity of the liver increases as much as 100% over the activity of the livers of normal lactating rats. Smaller increases (up to 31%) occur in anaerobic glycolysis of diabetic rat livers.

JACOBSEN, Buffalo.

ALLOXAN ADMINISTRATION IN THE GUINEA PIG. DOROTHY DOLE JOHNSON, Endocrinology **47**:393 (Dec.) 1950.

Restoration of the pancreatic islet tissue, which takes place within four days after alloxan administration in the guinea pig, is due to at least three factors: (1) transformation of peri-insular acinar cells by a process of redifferentiation into islet cells; (2) transformation of acini or parts of acini into new small islets; (3) proliferation of the epithelium of the smallest ducts to form new small islets.

JACOBSEN, Buffalo.

THE EFFECTS OF 17-HYDROXY-11-DEHYDROCORTICOSTERONE UPON THE ADRENALS OF NORMAL AND OF HYPOPHYSECTOMIZED RATS MAINTAINED WITH ADRENOCORTICOTROPIN. ROGER A. LEWIS, EUGENIA ROSEMBERG, and LAWSON WILKINS, Endocrinology **47**:414 (Dec.) 1950.

The daily administration of 1.25 mg. of cortisone acetate (compound E acetate) for 20 days to normal female rats causes a significant reduction in adrenal size and rise in adrenal cholesterol

concentration. Similar treatment of hypophysectomized female rats maintained with corticotrophin (ACTH) does not affect the adrenal size or cholesterol concentration. Adrenal atrophy produced by treatment with cortisone is caused chiefly if not entirely by inhibition of the production of corticotrophin.

JACOBSEN, Buffalo.

THE EFFECT OF HYPOPHYSECTOMY ON THE TOTAL CIRCULATING RED CELL VOLUME OF THE RAT. NATHANIEL I. BERLIN, DONALD C. VANDYKE, WILLIAM E. SIRI, and CHESTER P. WILLIAMS, Endocrinology **47**:429 (Dec.) 1950.

Studies on the influence of the pituitary on hematopoiesis have resulted in general agreement that after hypophysectomy there is a 30% anemia, as judged by a reduction in the hemoglobin concentration, red blood cell count, and hematocrit reading. The determination of the concentration of red blood cells and hemoglobin in the peripheral blood gives no real indication of the total circulating-red-cell volume, because of the possibility of the influence of changes in the blood volume. This study was designed to determine the changes in the total circulating-red-cell volume following hypophysectomy in the rat.

It was found that there was a decrease in the total red cell count to 45% of the value for normal animals. The factors concerned are discussed.

JACOBSEN, Buffalo.

EFFECT OF INSULIN INJECTIONS REPEATED AT BRIEF INTERVALS. MICHAEL SOMOGYI, Endocrinology **47**:436 (Dec.) 1950.

In previous articles the author presented experimental evidence to the effect that insulin action is self-inhibiting, and even self-terminating, as soon as it produces hypoglycemia. This phenomenon was ascribed to the mobilization by hypoglycemia of factors (in the main, hormones of the pituitary-adrenal system) which counteract insulin. This defensive mechanism goes promptly into action as soon as the blood sugar falls but a few milligrams below the normal fasting level, i. e., long before the onset of subjective symptoms of hypoglycemia. From this fact it follows that when insulin is injected in the postabsorptive state, the ensuing changes in the blood sugar do not truly represent the action of the injected insulin supply. This is so because the blood sugar declines below the fasting level immediately after injection, and this change, in turn, promptly mobilizes the insulin-antagonistic factors; the changes in the glycemic level, then, are contingent on a dynamic balance between the action of insulin in one direction and of its antagonists in the opposite direction, and the course of the blood sugar curve reflects the quantitative relation between insulin and its antagonists rather than the potential action of the supply of active insulin. In this paper it is shown that consecutive intravenous injections of small doses of insulin to healthy persons produce changes in the blood sugar level that present the mirror image of the changes produced by consecutive administrations of dextrose. The phenomenon following repeated dextrose feeding (Staub effect) is ascribed to stimulation of insulin secretion by hyperglycemia, with the consequence that the mobilized insulin holds down the hyperglycemic effect of successive dextrose doses. Insulin produces a counterpart of this picture: The initial insulin hypoglycemia stimulates the pituitary-adrenal mechanism to increased mobilization of insulin-antagonistic hormones, with the consequence that successive insulin doses exert considerably less hypoglycemic effect than the first. As a matter of fact, insulin action may be completely canceled by the antagonistic factors, which accumulate when hypoglycemia is allowed to persist for some time.

JACOBSEN, Buffalo.

THE TURNOVER OF BODY FAT IN OBESITY RESULTING FROM HYPOTHALAMIC INJURY STUDIED WITH THE AID OF DEUTERIUM. HAROLD MANKIN, J. A. F. STEVENSON, J. R. BROBECK, C. N. H. LONG, and DEWITT STETTEN JR., Endocrinology **47**:443 (Dec.) 1950.

The depot fat of the normal laboratory animal has been shown to participate in the "dynamic steady state" in that its molecules are known to be replaced by new molecules at relatively rapid rates. In the congenitally obese mouse, in contrast to the normal mouse, it was found that turnover of body fat was extremely slow. It was considered desirable to determine whether other forms of obesity were associated with the same slow turnover.

The obesity that follows surgical injury to the hypothalamus has been shown to be associated with a marked increase in food intake rather than with a diminution in the over-all metabolic rate. The present experiments were designed to measure the rate of turnover of the fatty acids of various body fats and to ascertain, if possible, whether this obesity resulted predominantly from excessively rapid deposition of fat or from abnormally slow mobilization.

The fraction and quantity of depot fat mobilized each day in obese rats was found to be extremely small but apparently not less than in the normal rat.

JACOBSEN, Buffalo.

TESTOSTERONE PREPARATIONS WITH PROLONGED ACTIVITY. W. J. EVERSOLE, JAMES H. LEATHEM, and HARALD SCHRAER, Endocrinology **47**:448 (Dec.) 1950.

Various preparations of testosterone were tested for duration of response. All of the preparations tested are much longer lasting in their effects than is the commonly used solution of testosterone propionate in oil.

JACOBSEN, Buffalo.

THYROID NEOPLASMS IN YOUTH. MORRIS E. DAILEY, and STUART LINDSAY, J. Pediat. **36**:460 (April) 1950.

Nodular goiters are likely to be neoplastic. Subtotal thyroidectomy should be performed in these cases in general. If malignancy is evident, radical thyroidectomy should be carried out, with removal of all involved lymph nodes. Long-term survival is possible even in the presence of metastases.

MACDONALD, Pittsburgh.

FOLLOW-UP STUDIES IN A BOY WITH MIXED ADRENAL CORTICAL DISEASE. LYTT I. GARDNER, RONALD C. SNIFFEN, ANIELA S. ZYGMUNTOWICZ, and NATHAN B. TALBOT, Pediatrics **5**:808 (May) 1950.

Supplementary data are presented concerning the metabolic and physical status of a boy with apparent mixed adrenal cortical disease. These data suggest that he has been suffering from (*a*) at least a relative deficiency of the adrenal cortical sodium-potassium-regulating hormone and (*b*) both a relative and absolute excess of adrenal cortical androgens. It appears that the adrenal cortical sugar-fat-nitrogen-regulating hormones were being produced in approximately normal amounts. The excess androgen production was associated with hyperplasia of adrenal cortical zone reticularis-like cells located in both the adrenals and the testes. It is suggested that the hyperplasia was the result of excess stimulation by corticotrophin. The effects of these derangements upon the patient's growth and development are described.

FROM THE AUTHORS' SUMMARY.

OBSERVATIONS ON PITUITARY-ADRENAL RESPONSE TO EPINEPHRINE: EOSINOPHIL DEPRESSION TEST. FORREST P. WHITE and LEE E. SUTTON JR., Pediatrics **5**:876 (May) 1950.

Results of the eosinophile-depression test, used as a test for normal function of the anterior lobe of the pituitary gland and adrenal cortex in response to stress, are consistent and valid in infants and children.

The pituitary-adrenal stress mechanism as judged by the eosinophile-depression test appears to be well developed in the full-term infant at birth. Newborn term infants showed normal responses. Premature infants with few exceptions failed to show a normal response to the test, indicating an immaturity in their resistance to stress as mediated by the anterior lobe of the pituitary gland and adrenal cortex. Older infants and children responded normally in 12 of 14 cases. Of the two exceptions, one was a child with eczema who had an intense eosinophilia and the other a child with diabetes insipidus.

Many clinicians have long held the belief that adrenal cortical hormones should be given to premature infants who do not respond to routine care or who are subjected to infection, operation, or other conditions of unusual stress. There is a need for further study of the therapeutic value of adrenal cortical hormones in premature infants with inadequacy of resistance to stress.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF DIABETES IN CHILDHOOD. A. LICHTENSTEIN, Archives Dis. Childhood **24**:237 (Dec.) 1949.

The author gives rather convincing reasons for "free diet" for diabetic children. The amount of insulin required is about the same as for children on restricted diet. Much emphasis is given to the psychological considerations favoring "free diet."

KELLY, Milwaukee.

ADRENAL NEUROBLASTOMA. R. WALLACE BOYD, Canad. M. A. J. **63**:153 (Aug.) 1950.

Six cases of adrenal neuroblastoma are reviewed. Attention is called to the difficulty of recognizing the disease until well-advanced metastases are present. Diagnosis requires careful correlation of clinical, roentgen, and pathological findings.

MCGUIGAN, Evanston, Ill.

ON PRENATAL CHANGES IN THE RELATIVE WEIGHTS OF THE HUMAN ADRENALS, THE THYMUS AND THE THYROID GLAND. ERIK EKHOLM and KALEVI NIEMINEVA, Acta pædiat. **39**:67, 1950.

The authors examined weight during the fetal period of the adrenals, the thymus, the thyroid gland, and, for purposes of comparison, the kidneys of fetuses up to 2,500 gm. and observed the following:

The adrenals were relatively largest at the fourth fetal month and the thyroid gland at the partus immaturus stage, whereas the thymus increased steadily. There was distinct diminution of weight after labor, greatest in the case of the thymus.

The weight of the endocrine glands of the different sexes, of twins, and of each half of a paired organ was examined. The glands in anencephalia, spina bifida, and hydrocephalus cases were also weighed.

The authors consider that the variations in the weight development of the different endocrine glands can no doubt be ascribed to their function during the fetal period.

FROM THE AUTHORS' SUMMARY.

A CASE OF PROGERONANISM (PROGERIA OF GILFORD). W. A. MANSCHOT, Acta pædiat. **39**:158, 1950.

The author gives further clinical description and a report of anatomic investigation of a case of progeronanism, already described by Schippers in 1916. The anterior lobe of the pituitary gland proved to be deficient in eosinophilic cells. This deficiency was demonstrated objectively by the method indicated by Rasmussen. Progeronanism should be regarded as a particular form of pituitary dwarfism, combined with inadequate development of tissue derived from the mesenchyme.

FROM THE AUTHOR'S SUMMARY.

THE SYNDROME OF PUBERTAS PRECOX, ADIPOSITY, POLYDACTYLY, OLIGOPHRENIA AND EPILEPSY ASSOCIATED WITH A LOCALIZED MALFORMATION IN THE HYPOTHALAMUS. B. BROUWER and R. BRUMMELKAMP, Folia psychiat. neurol. et neurochir. neerl. **51**:184 (Aug.) 1948.

Brouwer and Brummelkamp report the case of a man aged 20 with epilepsy, pubertas precox, mental deficiency, obesity, and polydactyly. Autopsy revealed a sharply circumscribed disturbance of development in the ventral portion of the hypothalamus. The tuber cinereum was hyperplastic, owing to increase of neuroglia and the intermediate tissue, and embryonic cells were observed in the same area. The number of normal ganglion cells in this region was greatly decreased, and there was an inhibition of development of various nuclear groups of the tuber cinereum. The medioventral hypothalamic nucleus could not be identified as such, and the mamillary bodies participated in the failure of development. They were small, deformed, and poor in cells. The cells of the perifornical nuclei were decreased in number, and the mamillothalamic bundle was poorly developed bilaterally.

The syndrome differed from the Laurence-Moon-Biedl syndrome in the absence of retinitis pigmentosa. The case is important because of the distinctly localized lesion which appears to have been responsible for the syndrome.

ALPERS, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

## Diseases of Muscles, Bones, Joints and Lymph Nodes

CLEIDOCRANIAL DYSOSTOSIS. H. ZELLWEGER, K. THEILER, and F. LARCHER, Helvet. paediat. acta **5**:264 (June) 1950.

An isolated case of cleidocranial dysostosis has been investigated by roentgenological and histological means. It was found that the disturbance effects both endochondral ossification at the epiphysis and metaphysis of long bones and membranous ossification of flat bones. The greatest disturbances were noticed in the ossification process of membranous bone. The observations suggest that resting cartilage hypertrophies by an increase in intercellular substance, compensating in this way, to some extent, for the lack of growth by normal ossification. However, as soon as most of the skeleton has become ossified and there is a reduction in the mass of resting cartilage, this compensatory mechanism fails, resulting in perpetual subnormal skeletal growth.

FROM THE AUTHORS' SUMMARY.

## Diseases of Eye

SIGHT RESTORATION IN A SCHOOL FOR THE BLIND. P. DORMAN, Am. J. Ophth. **32**:433 (March) 1949.

Dorman discusses restoration of sight under the headings of prenatal care, actual visual improvement, and psychologic adjustment. The article does not lend itself to abstraction.

W. S. REESE [ARCH. OPHTH.].

RETROLENTAL FIBROPLASIA: II. ENCEPHALO-OPHTHALMIC DYSPLASIA: STUDY OF 66 CASES. W. R. HEPNER, ARLINGTON C. KRAUSE, and HELEN E. NARDIN, Pediatrics **5**:771 (May) 1950.

Ninety-two per cent of the 66 patients with retrolental fibroplasia seen at the University of Chicago were born prematurely. No patients found to have retrolental fibroplasia were born at the Chicago Lying-in Hospital before 1937. The incidence of retrolental fibroplasia at the Chicago Lying-in Hospital from 1937 through 1945 was 6.8% in all survivals with weight less than 1,600 gm. at birth; from 1946 through 1948 the incidence was 30.4% in the same weight group. The ratio of surviving infants born weighing less than 1,600 gm. to the total number of surviving infants born at the Chicago Lying-in Hospital remained relatively constant from 1937 through 1948.

The etiology of retrolental fibroplasia cannot yet be explained by prenatal bleeding or specific infection. Cutaneous angiomas cannot be said to have etiologic significance in retrolental fibroplasia, since the incidence of cutaneous angiomas is no greater in infants with the disease than in premature infants in general. No relation between the use of sulfonamide drugs and the development of retrolental fibroplasia can be established in this series of patients.

An ocular disease of postnatal origin may be separated from the composite group. With this postnatal disease retinal detachment is the basic sign, prematurity is universal, and associated central nervous system and somatic defects are less common. A large increase in incidence of this postnatal disease occurred with a change in neonatal management. During the same period no change in the incidence of the disease of prenatal origin was apparent.

The one change in neonatal management that could be correlated with the increased incidence was the use of a multiple-vitamin preparation containing a synthetic emulsifying agent. An attempt to correlate the first appearance of or the changes in incidence of the disease at the University of Chicago with the first use of vitamin A or modification of the dosage of vitamin A was unsuccessful.

It is suggested that the title retrolental fibroplasia be reserved tentatively for those cases in which there is bilateral retinal separation as a complication of extreme prematurity until an etiologically appropriate name may be proposed.

FROM THE AUTHORS' SUMMARY.

PROPHYLAXIS OF OPHTHALMIA NEONATORUM WITH PENICILLIN. P. HALBRÓN, F. LEPAGE, C. LECOMTE, and H. MAWAS, Ann. ocul. **181**:676 (Nov.) 1948.

The authors review the treatment of ophthalmia neonatorum and cite the striking reduction in the incidence of this disease with the introduction of the use of silver nitrate. The dis-

advantages of silver nitrate are mentioned, especially its irritating effect on the conjunctiva. The efficacy of penicillin being well established, this substance was tried in 2,000 cases. Two drops of a penicillin solution containing 5,000 units per cubic centimeter was instilled in both eyes after birth. In their series there occurred one case of gonococcic conjunctivitis which responded promptly to penicillin therapy.

The authors conclude that penicillin is a safe prophylactic agent against ophthalmia neonatorum and that it is less irritating than silver nitrate.

P. R. McDonald [Arch. Ophth.].

Congenital Ectopia of the Lens with Spherophakia and Short Stature, Accompanied with Paralysis of Gaze (Marchesani's Syndrome). W. Stadlin and D. Klein, Ann. ocul. **181**:692 (Nov.) 1948.

Ectopia lentis is frequently associated with other congenital defects, as in Marfan's syndrome. Arachnodactyly is characterized by increase in length, laxness of ligamentous structures, and other congenital defects. Marchesani (1939) described another syndrome, characterized by brachydactyly, ectopia lentis, and spherophakia. Patients with this syndrome have round heads and short, stalky limbs, and the motility of their joints is normal.

The authors describe a patient who presented the signs and symptoms of this syndrome, as well as supranuclear paralysis of gaze. The genealogy of the patient is presented. The parents were second cousins; the mother was short and stocky, and the father had very small hands and feet. It is probable that the Marfan and the Marchesani syndrome differ only in that one shows hyperplastic and the other hypoplastic disturbances in the skeletal system. Schmid has linked the two conditions under the term "dysmorpho-dystrophia mesodermalis congenita."

P. R. McDonald [Arch. Ophth.].

## Cutaneous Diseases; Allergy

Poison Ivy: A Summary of One Hundred Cases Treated with Aqueous (Alum Precipitated Pyridine) Extract. G. Everett Gaillard, J. Allergy **21**:55 (Jan.) 1950.

One hundred and thirteen patients were treated with an aqueous alum-precipitated pyridine ivy extract. Most of them received injections of 0.4 and 0.8 ml. of 1:50 dilution, then 0.2, 0.6, and 1.0 ml. of 1:5 dilution at five to seven-day intervals and then 1.0 of 1:5 dilution at monthly intervals. Of the 113 patients, 77% had satisfactory results the first year of treatment; of 46 treated for two years, 84% had successful results the second season of treatment, and of 13 treated for three seasons, 92% had success the third season of treatment.

Hoyer, Cincinnati,

Dermatitis Following the Use of Pyribenzamine and Antistine. William B. Sherman and Robert A. Cooke, J. Allergy **21**:63 (Jan.) 1950.

Exacerbations of contact dermatitis were shown by skin tests to be due to tripelennamine (pyribenzamine®) hydrochloride ointment in two cases and in one case to antazoline (antistine®) hydrochloride drops. In the latter case a dermatitis medicamentosa due to tripelennamine developed when the drug was taken orally. In all three cases there was a history of allergy. The dermatitis occurred after the drug had been used for several days.

Separate tests were not made with the ointment base, since simultaneous tests with tripelennamine in the powder, cream, and ointment forms in each case showed the reaction to be greatest with the tripelennamine powder. Two of the patients reacted to other antihistamine drugs.

Hoyer, Cincinnati,

Loeffler's Syndrome with Skin Manifestations. Albert M. Jones, and Evelyn B. Ogle, J. Pediat. **35**:505 (April) 1950.

Jones and Ogle report a 2-yr.-old white boy with urticaria associated with Löffler's syndrome.

Macdonald, Pittsburgh.

ICHTHYOSIS FETALIS GRAVIS IN TWO SUCCESSIVE PREGNANCIES. WERNER BUSTAMANTE, and MARIO TEJEDA, J. Pediat. **36**:501 (April) 1950.

The authors report two cases of ichthyosis fetalis gravis in successive pregnancies. Both infants were premature; both died.

MACDONALD, Pittsburgh.

MOLLUSCUM CONTAGIOSUM TREATED WITH AUREOMYCIN. HERMANN VOLLMER, J. Pediat. **36**:797 (June) 1950.

A patient with molluscum contagiosum recovered promptly after treatment with aureomycin.

MACDONALD, Pittsburgh.

ERYTHEMA BULLOSUM MALIGNANS FOLLOWING DILANTIN THERAPY. GEORGE HELLER and MILTON SLOANE, Pediatrics **5**:836 (May) 1950.

A case of erythema bullosum malignans in a child 9 yr. of age is presented. In this patient, as in two other cases to which reference is made, there was a history of administration of diphenylhydantoin (dilantin®) sodium for several weeks prior to the illness, then an acute onset with prostration, chills, high fever, and a generalized hemorrhagic bullous eruption, with involvement of the orificial and conjunctival mucous membranes.

The possibility of diphenylhydantoin medication having been the causative factor in this and other similar cases is discussed. It is stressed that, because of the severe reaction of toxemia and shock present in this self-limited disease, antibiotic agents and intravenous alimentation, especially the free use of whole blood, may be lifesaving in tiding the patient over the protracted period of hypoproteinemia caused not only by weeping from the skin surface but also by loss of substance from unrecognized visceral lesions.

FROM THE AUTHORS' SUMMARY.

ANTIHISTAMINIC THERAPY OF ALLERGIC DISORDERS IN INFANTS AND CHILDREN. I. NEWTON KUGELMASS, New York J. Med. **49**:2313 (Oct. 1) 1949.

The purpose of this study of 309 infants, children, and adolescents was to note the influence of diphenhydramine hydrochloride (benadryl hydrochloride®), methaphenilene hydrochloride (diatrine hydrochloride®), and tripelennamine hydrochloride (pyribenzamine hydrochloride®) on allergies. In cases of gastrointestinal allergies it was necessary first to get rid of the offending allergens before the drugs could be effective. The therapeutic effect was least in the newborn and most in older children. Hay fever in season (mild type) was controlled by antihistaminics alone. In severe forms specific immunization was a necessary ancillary procedure.

Vasomotor rhinitis was not alleviated by antihistaminics until clearance of the multiple allergens was completed. The recurrent type responded better than the chronic type. Bronchial asthma was benefited in the primary hereditary form and occasionally in the secondary acquired type but not at all in the pulmonary residual-injury type. Methaphenilene worked better for cough but was less effective for dyspnea and wheezing.

The skin manifestations, pruritus, acute edema (angioneurotic), serum sickness, and drug dermatitis, were alleviated symptomatically. Dosage of all three drugs was evaluated according to body weight and severity of symptoms. Acute toxic reactions were seen in about 25% of all cases, but they disappeared completely after withdrawal of the drug. The symptoms were drowsiness and nervous and digestive disturbances, but no blood alterations. Methaphenilene was more effective in small doses and better tolerated than tripelennamine. The latter drug was better tolerated than diphenhydramine at each age level. Six tables serve to illustrate the therapeutic values of each drug.

I. W. VOORHEES, New York [ARCH. OTOLARYNG.].

# News and Notes

## GENERAL NEWS

**Specialists Certified by American Board of Pediatrics, Inc.**—The following physicians were certified as specialists by the American Board of Pediatrics, Inc., after examinations held in Detroit on June 8, 9, and 10, 1951:

Bacon, A. Maynard, Jr., Baltimore.
Becker, George H., St. Louis.
Beesley, James Chester, Lancaster, Ohio.
Bellin, Leonard Bernard, Providence, R. I.
Brodsky, William A., Louisville.
Bryan, Eunice Elizabeth, Seattle.
Bush, Louis G., Pocatello, Idaho.
Butler, Hugh H., Rochester, N. Y.
Cale, Ellsworth Ferrell, Atlanta.
Cobley, George Gordon, Camp Edwards, Mass.
Cochran, Quinten Wood, Portland, Ore.
Coleman, Allan Bertram, Washington, D. C.
Cone, Thomas E., Jr., Princeton, N. J.
Davis, Marvin L., Alhambra, Calif.
Eagle, J. Frederick, Jr., Buffalo.
Feeley, Marshall John, St. Joseph, Mich.
Forman, Carolyn Wood, New York.
Gajdusek, D. Carleton, Boston.
Goebel, Carl William, Ft. Wayne, Ind.
Goodwin, Marvin Harold, Beverly Hills, Calif.
Green, Morris, Chicago.
Hellmann, Charles H., Glen Head, N. Y.
Hodes, Louis, New York.
Hoogerland, Clarence L., Alma, Mich.
Karpinski, Felix E., Jr., Cleveland.
Kessler, Walter Richard, New York.
Krauss, Ruth F., Kenmore, N. Y.
Lasell, Sidney L., Pasadena, Calif.
LeBien, Wayne E., Fargo, N. D.
Line, Felix G., Knoxville, Tenn.
McCloskey, George Albert, Rochester, Pa.
Meyers, Lewis, Kalamazoo, Mich.
Middleton, Thomas O., Bloomington, Ind.
Miller, Harold R., Memphis.
Nichols, Howard H., Nashville, Tenn.
Nierenberg, Marvin, Chicago.
Paul, Raphael N., Memphis.
Pelegrin, Ralph John, Cleveland.
Phillips, Donald Charles, Wenatchee, Wash.
Piel, John Joseph, San Francisco.
Reuben, Richard N., New York.
Riedy, Thomas F., Jr., Albany, N. Y.
Schifrin, Nathan, New York.
Shelden, Warren Earl, Detroit.
Siegel, Sheldon C., St. Paul.
Startzman, Viola V., Wooster, Ohio.
Stitt, Donald Golder, Waynesburg, Pa.
Tobolowsky, Dave, Dallas, Texas.
Tolmas, Hyman C., New Orleans.
Warthen, Robert Orr, Kensington, Md.
Williams, Starks Johnson, Chicago.

**Chicago Pediatric Society Third Annual Resident's Competition.**—In the Third Annual Resident's Competition of the Chicago Pediatric Society, held on April 17, 1951, Drs. Elmer R. Kadison and Howard S. Traisman tied for first place with "The Treatment of Infantile Diarrhea with a New Combination of Antibiotics" and "The Use of Desoxycorticosterone Acetate in Dehydration and Malnutrition in Infancy" respectively, and Dr. C. R. Castaldi (D.D.S.) won third place with "Acute Infectious Gingivo-Stomatitis (Herpetic Stomatitis) and Its Response to Oral Administration of Aureomycin."

## ANNOUNCEMENTS

**Twentieth Annual Benjamin Knox Rachford Lectures.**—Sir James Spence, M.D., Director of the Department of Paediatrics and Nuffield Professor of Child Health, King's College, Newcastle, England, will deliver the twentieth annual series of the Benjamin Knox Rachford Lectures on Thursday, Nov. 1, and Friday, Nov. 2, 1951, at 8:30 p. m., in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. The titles of his lectures are (1) "The Experience of the Universities in Medical Education" and (2) "The Experience of Paediatrics in the Universities."

**Annual Meeting of the American Academy for Cerebral Palsy.**—The American Academy for Cerebral Palsy will hold its annual meeting in Boston, at the Copley Plaza Hotel, on Friday and Saturday, Nov. 16 and 17, 1951. The Friday afternoon scientific session will be open to all interested physicians, and the program will include the following: "The Cerebral Palsy Problem in 1951," Dr. Bronson Crothers, President; "Physiology of Motor Learning as Applied to Cerebral Palsy," Dr. Frances Hellebrandt; "Studies of Gait Patterns of the Hemiplegic Patient," Dr. Morton Marks; "Surgical Methods for Functional Improvement of the Hand in Spastic Paralysis," Dr. William Cooper; "Diastematomyelia," Dr. Franc Ingraham, and "Paradoxical Benefit of Cortical Ablation for Selected Hemiplegics," Dr. Wilder Penfield.

**Catologue on Medical Motion Pictures.**—A revised catalogue of motion pictures available through the Committee on Medical Motion Pictures of the American Medical Association is now available. Copies will be sent to the secretary of each county and state medical society. This catalogue lists sixty-two 16-mm. films, most of which are at the professional level. Fourteen of these films are suitable for showing to lay groups. Eight new films have been added. Copies are available upon request from Committee on Medical Motion Pictures, American Medical Association, 535 N. Dearborn St., Chicago 10.

**Third Maurice Lamm Blatt Memorial Fund Lecture.**—The pediatric staff of the Cook County Hospital announces the Third Maurice Lamm Blatt Memorial Fund Lecture by Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics, University of Minnesota, who will talk on "Clinical and Experimental Studies on Hypoglycemia."

This lecture will be given Tuesday, Oct. 2, 1951, at 8:30 p. m. in the medical amphitheater of the Cook County Hospital. All interested physicians are invited to attend.

**American Association for the Advancement of Science.**—The American Association for the Advancement of Science will hold its meeting in Philadelphia, Dec. 26 to 31, 1951.

**Texas Pediatric Society.**—The Texas Pediatric Society will hold its annual meeting at the Rice Hotel in Houston, Texas, Oct. 12 and 13, 1951.

**Coming Examinations to be held by the American Board of Pediatrics, Inc.—**The American Board of Pediatrics, Inc., will hold oral examinations on Oct. 26, 27, and 28, 1951, in Buffalo and in early December, 1951, in Chicago.

## PERSONAL

**Dr. Thomas E. Shaffer and Dr. Samuel L. Cresson Join St. Christopher's Hospital for Children.**—Dr. Thomas E. Shaffer, formerly with the Departments of Pediatrics and Preventive Medicine at Ohio State University, Columbus, Ohio, has taken up his duties as Professor of Preventive Pediatrics at Temple University School of Medicine and Coordinator of Community Activities for St. Christopher's Hospital for Children, Philadelphia.

Dr. Samuel L. Cresson has joined the staff of St. Christopher's Hospital for Children, in the Division of Surgery. Dr. Cresson will limit his practice to infants and children.

**Appointment for Dr. Samuel M. Wishik.**—Dr. Samuel M. Wishik has been appointed Professor of Maternal and Child Health in the Graduate School of Public Health of the University of Pittsburgh.

# Book Reviews

**Lehrbuch der Kinderheilkunde.** By R. Degkwitz, E. Glanzmann, F. Goebel, J. Jochims, K. Klinke, F. Klose, E. Rominger, and B. de Rudder. Fourth and fifth revised edition, edited by E. Rominger. Price, 49.80 marks. Pp. 971, with 267 illustrations, some colored. Springer-Verlag, Reichpictschufer 20, Berlin W. 35 (Britische Sektor), 1950.

The writing of the subject matter of this textbook of pediatrics is distributed among a number of well-known contributors. Jochims starts with "Growth and Development" and "Medical Supervision of the Healthy Child." It is stated here and in a later chapter by de Rudder that there has been an acceleration of the growth of the youth of today and an advent of sexual maturity at an earlier age. The development of the static, psychic, and mental function is also given. Degkwitz, in the chapter on "The Education of Healthy Children," states that he regards it essential that proper somatic development is assured and also that the infant be taught that it is a part of everyday life to bear unpleasant feelings without undue emotional discharges. Also it is recommended that a strict regimen of care and feeding be adhered to. Such a regimen should not be carried further than the first half of the second year, when the infant begins to develop into an individual acting and willing independently.

This chapter has features not in accordance with ideas prevailing in this conutry. Maybe here also more than one road leads to Rome, and at times it may be that the administration of a given regimen is as important as the regimen itself. De Rudder, in the next chapter, deals with "Susceptibility to Disease, the Danger of Diseases and Child Mortality." Constitution and constitutional disease are discussed, including the influence of hereditary and environmental factors. A little slip attributes chemical mutation to mustard gas (dichlorodiethyl sulfide) instead of to nitrogen mustard (methyl-*bis* or *tris* [2-chloroethyl] amine hydrochloride). "The Care of the Health in Childhood" is presented by Klose, together with the legal provisions for the welfare of mother and child. "The Examination of the Sick Child" by Rominger is followed by "The Acute Infectious Diseases of Childhood" by Degkwitz, who stresses the influence of the state of civilization on their frequency and on the age period at which they occur. The bearing of the concentration of persons in the domicile on the spread of infections is emphasized particularly. When it becomes advisable to protect children against measles and convalescent serum is not available, it is recommended that twenty to thirty milliliters of fresh adult whole blood be injected intramuscularly, obviating the necessity of grouping. But it has been demanded of late that even so the Rhesus factor should not be neglected. The material on Roseola infantum could stand a little more elaboration. The administration of diphtheria antitoxin is demanded on suspicion of the disease, because diphtheria toxin is anchored rather rapidly to tissues, while antitoxin remains in the circulation much longer, and toxin attached to the tissues is no longer neutralized by antitoxin, so that antitoxin even when given intravenously can only prevent further damage. The seeming resistance of malignant diphtheria to antitoxin is also explained. The conception of the Dicks that a hemolytic streptococcus is endowed with the power to produce a specific scarlet fever toxin responsible for the skin rash is not accepted, since streptococci of various origins are said to produce the same toxin as the scarlet fever streptococci and an infection with toxin-producing streptococcus need not lead to scarlet fever. Only under certain conditions, hitherto unknown, is this the case. The work of Bingel may be of interest in this connection. He concluded that a streptococcus virus combination is necessary for the production of scarlet fever. The diagnosis of Bang's disease is said to be assured by the specific agglutination test. It should not be omitted that in acute cases a positive blood culture is the only reliable proof of the disease. This part of the volume ends with a short description of "Toxoplasmosis," to which in a later edition histoplasmosis should be added. "Tuberculosis in Childhood" is presented by de Rudder. BCG vaccination is credited with definite success, in small print. "Syphilis of the Child" is contributed by Goebel, who gives some detailed directions for treatment, with inclusion of mercury preparations, while a footnote recommends that such preparations be avoided whenever possible. The same author deals with the "Diseases of the Newborn Infant." In regard to nutritional disturbances of the newborn

it is stated that the newborn infant must have human milk. "Metabolism and Nutrition of the Healthy Infant" fell to the share of Rominger. It is acknowledged that the mortality among artificially fed infants during the first months of life does not differ significantly from that of breast-fed infants. But artificial feeding is held to be the most important cause of the avoidable diseases of the infant for a period up to five months. Directions are given for artificial feeding. The same author contributes "The Nutritional Disorders of the Infant." Although a really satisfactory classification of the nutritional disorders is not yet possible, a rather widely accepted classification is given: (1) acute disorders of nutrition of the artificially fed infant (*a*) mild: dyspepsia, (*b*) severe: toxicosis; (2) chronic disorders of nutrition (*a*) mild: dystrophy, (*b*) severe: pedatrophy. The disorders of nutrition of the breast-fed infant are (1) dyspepsia, (2) deficient progress, and (3) constipation. Dystrophy and pedatrophy are described together. The high caloric feeding of the atrophic infant is not mentioned. In the following part Rominger takes up "Metabolism and Nutrition of Older Children"; in the next, "The Diseases of Metabolism of the Older Child," that is, of preschool and school age, and in the next, "Avitaminoses and Hypovitaminoses." Hypervitaminoses should not be omitted. "Diseases of the Glands of Internal Secretion" by Glanzmann starts off with diseases of the thymus. Roentgenograms are taken before and after treatment of a "hyperplastic" thymus with x-rays, to demonstrate the effected diminution of its size. But it seems that the roentgenogram taken after treatment is taken in inspiration, that before treatment in expiration, so that is hardly permissible to compare the two pictures. The same author writes about the "Diseases of the Blood." In his opinion the majority of the acute leukemias of children belong to the myeloses, as in the adult, for reasons given. Jochims writes about the "Diseases of Mouth, Nose and Throat, and Pharynx" and Klinke about the "Diseases of the Respiratory Tract." Among the causes of stridor of the young infant might be included the double arch of the aorta and the atony of the larynx. In the chapter on "Diseases of the Organs of Digestion" Goebel includes anorexia and abdominal pains. Regional enteritis should find a place here. "Acute, Hemorrhagic Necrosis of the Small Intestine" (jejunitis necroticans) should be of special interest in this country. It had been described before its increased incidence in 1946. In the treatment of ascariasis (Ascaris lumbricoides), hexylrescorcinol is not mentioned. "Diseases of the Circulation" are discussed by Klinke. Hypertension is treated rather shortly. It might be mentioned that some patients with a hyperplastic kidney can be benefited by removal of this kidney. Enuresis is included in the chapter on "Diseases of the Urinary and Genital Organs." It should be recognized that enuresis cannot be fully understood so long as the physiology of micturition is not fully understood. This lack of understanding reflects itself clinically, perhaps, in the percentage of patients who resist all treatment. The claim that the effect of drugs is nearly always due to suggestion cannot be upheld by the example of atropine, which, under certain conditions, can influence the capacity of the bladder. Under sulfonamide treatment, the micro-organisms may disappear from the urine later than the leucocytes, but this can hardly be accepted as a sign that these drugs do not act as urinary disinfectants but rather that they act on the inflammation.

The bacteriostatic and bactericidal power of these drugs has been established. It might also be mentioned that for instance colon bacilli may overgrow others so that these have to be demonstrated by special examinations. Glanzmann depicts the "Pathology of Growth and Development." Under the heading of "Diseases of the Organs of Motion" Degkwitz includes acute rheumatism. He objects to the designation "polyarthritis acuta," at least for children, as placing a completely unessential symptom in the forground, unessential for the nature and cause of the disease. These reasons may not be regarded as very convincing. Goebel, in "Diseases of the Nervous System," tabulates conveniently the results of various tests of the cerebrospinal fluid in various diseases of the central nervous system. Degkwitz follows with "The Education and Treatment of Neuropathic and Psychopathic Children." "Diseases of the Skin" are described by Goebel. Under the heading "General Therapy," Rominger gives instructions with regard to hydrotherapeutic measures, washing out of the stomach, intestines, and bladder, the use of dry heat and of dry cold, and others. The same author deals with "Drug Therapy in Childhood." An extensive table lists the drugs alphabetically, the dosage at the ages of 4 to 12 months, 3 to 4 years, and 8 to 10 years. Under remarks, the character of the drug is given. This is particularly useful, since the drugs are often listed under their trade names. Sometimes the use of the drug and its dangers are given.

The book is rather comprehensive and represents German pediatric teaching very well, as could be expected from the prominence of the authors. Such a book is bound to contain some errors, some of which have been mentioned. On the whole, they are neither numerous nor serious. Some readers, no doubt, would like to see more space given to illustrative cases and less to theoretical considerations, however stimulating. The book can be recommended without hesitation.

**Adrenal Cortex: Transactions of the First Conference, November 21-22, 1949.** Edited by Elaine P. Ralli; associate editors, Konrad Bloch and Gregory Pincus. Price, $2.00. Pp. 189, with 21 figures. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1950.

In November, 1949, the Josiah Macy, Jr., Foundation brought together for a two-day conference on the adrenal cortex a group of outstanding investigators from various branches of science. This volume is a verbatim record of their informal discussions as they explored the physiological and biochemical alterations associated with the administration of adrenal cortical hormones in an effort to determine their value.

To anyone interested in this field the following list of those who shared their research experiences in the round-table discussions will suffice to indicate the high scientific level of the material contained in this small volume: C. N. H. Long, New Haven, Conn.; Elaine P. Ralli, New York; Walter Bauer, Boston; Konrad Bloch, Chicago; J. W. Conn, Ann Arbor, Mich.; E. Gellhorn, Minneapolis; Dwight W. Ingle, Kalamazoo, Mich.; Edward C. Kendall, Rochester, Minn.; Choh Hao Li, Berkeley, Calif.; Robert F. Loeb, New York; Gregory Pincus, Shrewsbury, Mass.; Robert F. Pitts, Syracuse, N. Y.; George Sayers, Salt Lake City, Utah; Hans Selye, Montreal, Que.; George W. Thorn, Boston; Abraham White, Los Angeles.

Discussion centered around the following topics: (1) relation of chemical structure to biological activity; (2) regulation of secretion; (3) clinical use of cortisone and corticotrophin (ACTH); (4) steroid metabolism in adrenal cortex, and (5) relation of vitamins to adrenal cortical function.

While this book is not intended as a guide to the clinical use of cortisone and corticotrophin, it would be well if every clinician who expects to use these substances would read it, if for no other purpose than to gain some idea of their tremendous potentialities for widespread and varied effects, both beneficial and detrimental. Although much of the material is of a highly technical nature, the manner of presentation, with remarks of the participants set down just as they were made, makes for easy reading. The reviewer has the feeling that this is in general a better way to present most subjects than by means of the usual dry-as-dust article, in much the same way as bedside teaching is superior to a didactic lecture.

For those carrying on research of an endocrine nature this volume is a gold mine of information.

**Freud: Dictionary of Psychoanalysis.** Edited by Nandor Fodor and Frank Gaynor, with preface by Theodore Reik. Price, $3.75. Pp. 220. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1950.

This book presents in glossary form the basic terms of psychoanalysis as defined by Freud himself in his original writings. It is an attempt to present in one easily accessible place the original definitions of terms by the founder of psychoanalysis and such modifications or amplifications as occur in his later writings. For the individual student or practitioner to search these out in Freud's voluminous works takes a great deal of time and is well nigh impossible for most. It often becomes important to know just what a term introduced by Freud does mean or how the original meaning was modified. Psychoanalysis in its popularization was subjected to a good deal of misconception and distortion. The misunderstandings and misinterpretations of what Freud really said add to confusion both within and without the field of medical psychology. This book should help to clear up some of this confusion.

The editors carefully studied all of Freud's writings, and the most informative definitions of terms and concepts are incorporated in this glossary in his own words. Great care was taken to avoid taking a phrasing of a definition out of context. Where there have been varieties of application these have been presented in subheadings. Each quotation is identified as to its source.

It is a worth-while, scholarly attempt which should meet a real need. It should be a convenient and useful reference work for the psychoanalyst, psychiatrist, psychologist, or others professionally working with emotionally disturbed persons. The pediatrician attempting to utilize concepts, skills, and insights from medical psychology in his practice of comprehensive pediatrics should find this book helpful as he is confronted, in his search for additional knowledge, with new and confusing terms. Here he will find them defined in an authoritative setting.

**A Syllabus of Laboratory Examinations in Clinical Diagnosis.** Edited by Thomas Hale Ham, M.D. Price, $5.00. Pp. 496, with numerous figures and charts. Harvard University Press, Cambridge 38, Mass., 1950.

This paperbound, lithographed volume was produced as part of the second-year course in laboratory diagnosis at Harvard University. Correlation of laboratory tests with the history and physical examination is emphasized, and throughout the book the various procedures are discussed from the point of view of clinical value, availability, cost, principle, method, and limitations and interpretations of the test itself and as a diagnostic aid related to the history and physical examination of the patient.

The book is divided into seven sections. The first is an introduction to laboratory examinations, including units of measure and tables of normal values, costs of various procedures, and a chapter on laboratory data in clinical medicine. The last deals with the choice of procedures, qualitative, semiquantitative, and quantitative determinations, errors and their source. It is something that should be read carefully by all physicians and is not likely to be found elsewhere.

Section four is an extremely comprehensive consideration of hematologic studies. The other sections cover urinary and gastrointestinal systems, infectious diseases, metabolic disorders, and extravascular fluids.

No fault can be found with the material included in this book; there is much that could be found elsewhere only by intensive search. Although the book was written for students, it should be of the greatest value to all practising physicians.

**The Physician Examines the Bible.** By C. Raimer Smith, B.S., M.D., D.N.B. Price, $4.25. Pp. 394, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1950.

"The Physician Examines the Bible" proves one thing and that is that Dr. C. Raimer Smith is thoroughly familiar with his Bible. His conclusion "that the Bible is so accurate from the medical standpoint" is too often based on a forced interpretation of texts and is scarcely warranted at any point by our present-day knowledge of the conditions under which medicine was practiced in Bible times.

After all, the age-old definition that "faith is the substance of things hoped for, the evidence of things not seen" remains as today's truth. The conflict that has persisted in all times between science and the Bible has not been disturbed by Dr. Smith. The Bible lives in men's hearts as an expression of faith and of human needs—and would lose much of its authority if it were a mere recital of demonstrable facts.

The volume has a value to the revivalist and as an appeal to the emotions, but it is not required reading for those who seek to prove a point of view which includes the teaching of quality medical care. The truth of the matter is that the Bible is not helped by attempts to dress up its truths into something that it never intended to teach.

# Directory of Pediatric Societies *

## INTERNATIONAL

### International Pediatric Association

President: Dr. Felix Hurtado, Habana, Cuba.
Secretary: Dr. Guido Fanconi, Kinderklinik, Zurich, Switzerland.
Next Meeting (Seventh International Congress of Pediatrics): Habana, Cuba, 1953.

### International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

### Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

### International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quay Wilson, Geneva, Switzerland.

## FOREIGN

### Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriquez Peña.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179.

### Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393. 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

### Asociación Pediatrica de Guatemala

President: Dr. Carlos Manuel Monzon, Plazuela Santuario de Guadalupe, Guadalupe.
Secretary: Dr. Maria Isabel Escobar, Casa del Niño no. 1, Guadalupe.

### Australian Paediatric Association

President: Dr. H. Douglas Stephens.
Secretary-Treasurer: Prof. Lorimer Dods, The Institute of Child Health, Royal Alexandra Hospital for Children, Camperdown, N. S. W., Australia.
Time: One meeting a year.

### British Paediatric Society

President: Dr. A. G. Maitland-Jones.
Secretary: Dr. Alan Moncrieff, Institute of Child Health, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

### Bulgarian Pediatric Society

President: Dr. L. Ratchew, University Children's Hospital, Wassil Kolarow 46, Sofia.

### Chinese Pediatric Society

President: Dr. Fu-tang Chu, Peking Children's Hospital, Peking, China.
Secretary: Dr. Hua-kang Chow, Peking Union Medical College, Peking, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

### Czechoslovak Pediatric Society

Chairman: Prof. Dr. Jiri Brdlík, 2 Sokolská, Prague II.

### Danish Pediatric Society

Chairman: Prof. Preben Plum.
Secretary: Dr. Elin Fog, Søllingsvey 17, Charlottenlund, Denmark.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

GERMAN PEDIATRIC SOCIETY

President: Dr. H. Kleinschmidt.
Secretary: Dr. F. Goebel, 5 Moorenstrasse, Düsseldorf, Germany (British Zone).

HELLENIC SOCIETY OF PEDIATRICS

President: Dr. C. Saroglou, Patission St. 74, Athens, Greece.
Secretary-General: Dr. S. Charocopos, Alexandras Ave. 1, Athens, Greece.

INDIAN PEDIATRIC SOCIETY

President: Dr. K. C. Chaudhuri, Dept. of Pediatrics, Medical College, Calcutta.
Secretary: Dr. S. P. Bhattacharjee, Dept. of Pediatrics, Medical College, Calcutta.
Place: Office of the Indian Medical Association, 67 Dharamtala St., Calcutta 13.
Time: Every second and fourth Wednesday of each month.

MEDICAL ASSOCIATION OF ISRAEL, NATIONAL PEDIATRIC SOCIETY

President: Prof. L. F. Meyer, 29 Idelson St., Tel-Aviv, Israel.
Secretary: Dr. W. Hirsch, Hadassah Municipal Hospital, Tel-Aviv, Israel.

NEDERLANDSCHE VEREENINGING VOOR KINDERGENEESKUNDE

President: Dr. G. J. Huët, 39 Brediusweg, Bussum.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

NORWEGIAN PEDIATRIC SOCIETY

President: Dr. Arne Njå, Oslo.
Secretary-Treasurer: Dr. Helge Granrud, Abbedikollen 38, Bestun, Oslo.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

See Medical Association of Israel, National Pediatric Society.

PEDIATRIC SOCIETY OF NEW ZEALAND

President: Dr. Lawrence Ludbrook, The Lister Building, Victoria Street East, Auckland.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Dr. Kenneth Tallerman.
Secretary: Dr. I. M. Anderson; Dr. Ronald MacKeith.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SCHWEIZERISCHE GESELLSCHAFT FÜR PÄDIATRIE

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela D., Casilla 272, La Paz, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

SOCIEDAD CHIHUAHUENSE DE PEDIATRIA

President: Dr. Carlos Villamar Talledo.
Vice President: Dr. H. Uranga.
Secretary: Dr. Reynaldo Ramos Varela.
Treasurer: Dr. David Russek.
Place: Children's Hospital, Matamoros St., Chihuahua, Chihuahua, Mexico.

SOCIEDAD CHILENA DE PEDIATRIA

Secretary-General: Dr. Oscar Undurraga A., Merced 565, Santiago, Chile.
Place: Medical Society, Merced 565, Santiago, Chile. Time: 7 p. m., every Thursday.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Miguel Fabres Izaga.
President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21. Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Jaime Jorge, Jose Joaquin Perez, no. 25, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Alberto Peguero, V., Ave. Bolivar 113, P. O. Box 464, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

SOCIEDAD ECUATORIANA DE PEDIATRIA

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Gabriel Araujo Valdivia.
Vice-President: Dr. Ramón Pous Roca.
Secretary: Dr. Luis Torregrosa F.
Corresponding Secretary: Dr. Antonio Prado Vertiz.
Treasurer: Dr. Fernando López Clares.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.).
Place: Comite pro Defenso del Niño, Dean Fumes 2000.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDADE PORTUGUÊSA DE PEDIATRIA

President: Prof. Castro Freire.
Secretary-Generale: Dr. Cordeiro Ferreira, Hospital de D. Estefania, Lisbon, Portugal.

SOCIEDAD URUGUAYA DE PEDIATRIA

President: Dr. Conrado Pelfort.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Lya Imber Coronil.
Secretary: Dr. Guillermo Tovar, P. O. Box 5, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE MONTRÉAL

President: Dr. Paul Letondal, 370 E. Roy St., Montreal, Quebec, Canada.
Secretary-Treasurer: Dr. Edmond Baril, 301 Carré Saint-Louis, App. 1.
Time: First and Third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of each month.

SOCIÉTÉ DE PÉDIATRIE DE QUÉBEC

President: Dr. Roland Thibaudeau, 203 des Erables, Quebec, Que., Canada.
Secretary-Treasurer: Dr. Euclide Déchêne, 312 du Roi.

SOCIETÉ POLONAISE DE PÉDIATRIE

President: Dr. Jan Bogdanowicz, Dzialdowska 1, Warsaw.
Secretary: Dr. Zofia Leimbach, Mieroslawskiego 9 m.6, Warsaw.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH ASSOCIATION OF PEDIATRICS

President: Prof. Sture Siwe, Lund.
Secretary: Dr. K. A. Melin, Färjestadsvägen 16, Bromma.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Docent H. Magnusson, Sachs' Hospital for Children, Stockholm.
Secretary: Dr. M. d'Avignon, Norrtulls Sjukhus, Stockholm.
Place: Swedish Medical Society, Klara Östra Kyrkogata 10, Stockholm and Pediatric Clinic Upsala. Time: Second Friday of each month (except summer).

VIENNA PEDIATRIC SOCIETY

President: Prof. Dr. A. Solé, Karolinen-Kinderspital, Sobieskigasse 31, Vienna 9.
Secretary: Doz. Dr. Asperger, Universitäts-Kinderklinik, Lazarettgasse 14, Vienna 9.

## NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester 7, New York.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Annual Meeting: Place: Toronto, Canada. Time: Oct. 20-25, 1951.*

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Horace Hodes, New York.
Secretary-Treasurer: Dr. Sydney S. Gellis, 300 Longwood Ave., Boston 15.

## SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

* The time and place of this meeting were incorrectly given in the January issue.

### New England Pediatric Society

President: Dr. Henry E. Gallup.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Time: Four meetings a year.

### North Pacific Pediatric Society

President: Dr. Gordon O. Matthews, 808 Medical-Dental Bldg., Vancouver, B. C.
Secretary-Treasurer: Dr. S. Gorham Babson, 1220 S. W. Taylor St., Portland, Oregon.

### Northwestern Pediatric Society

President: Dr. J. Harry Murphy, 915 Medical Arts, Bldg., Omaha.
Secretary-Treasurer: Dr. Elizabeth Lowry, 301 Kenwood Parkway, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

### Rocky Mountain Pediatric Society

President: Dr. Joseph Lyday, 227 16th St., Denver 2.
Secretary-Treasurer: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of Denver or the Colorado General Hospital. Time: Monthly from October to June.

### Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

### Southwestern Pediatric Society

President: Chester I. Mead, 1930 Truxton Ave., Bakersfield, Calif.
Secretary: Dr. Clement H. Molony, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

## STATE

### Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6.

### Arizona Pediatric Society

President: Dr. Carl A. Holmes, 1401 N. 7th Ave., Phoenix.
Secretary-Treasurer: Jacob M. Sobol, 607 Heard Bldg., Phoenix.
Place: Phoenix or Tucson. Time: On Call.

### Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

### California State Medical Society, Section on Pediatrics

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.

### Florida State Pediatric Society

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

### Georgia Pediatric Society

President: Dr. Howard J. Morrison, 444 Drayton St., Savannah.
Secretary-Treasurer: Dr. J. Harry Lange, 490 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

### Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SOCIETY

Chairman: Dr. Thurman B. Givan, 115 Remsen St., Brooklyn 2.
Secretary: Dr. Reginald A. Higgons, Port Chester.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert J. Mason, 308 N. Woodward Ave., Birmingham.
Secretary: Dr. Horace L. French, 301 Seymour Ave., Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

MONTANA PEDIATRIC SOCIETY

President: Dr. Edward A. Hagmann, 208 N. Broadway, Billings.
Secretary: Dr. George W. Nelson, 2814 9th Ave. N., Billings.
Place: Decided at each meeting—Spring and Fall.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. George E. Stafford, 823 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. Donald C. Nilsson, 115 North 40 St., Omaha.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. Edward L. Tuohy, Manchester.
Secretary-Treasurer: Dr. William D. Penhale, Concord.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.
Secretary: Dr. N. T. Crane, 147 E. 7th St., Plainfield.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Rowena Sidbury Hall, 15 N. 5th St., Wilmington.
Secretary-Treasurer: Dr. Katherine Anderson, 138 Hawthorne Rd., Winston-Salem.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

### North Dakota Pediatric Society

President: Dr. L. G. Pray, Fargo Clinic, Fargo.
Vice President: Dr. B. A. Mazur, Dakota Clinic, Fargo.
Secretary-Treasurer: Dr. William J. Ball, Northwest Clinic, Minot.
Place: Bismark.

### Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

### Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Philippine General Hospital, Manila.
Secretary: Dr. Artemio P. Jongco, Philippine General Hospital, Manila.
Place: Philippine General Hospital. Time: Every two months.

### South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

### Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

### Texas Pediatric Society

President: Dr. Thomas D. McCrummen, 304 Capitol Nat'l Bank Bldg., Austin.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave., Waco.
Treasurer: Dr. Edith Bonnet, 228 Medical Arts Bldg., San Antonio.

### Virginia Pediatric Society

President: Dr. E. Berkeley Neal.
Vice President: Dr. E. L. Kendig.
Secretary-Treasurer: Dr. W. A. Mitchell.
Executive Board: Dr. F. R. Hopkins and Dr. J. O. Rydeen.

### Wisconsin State Medical Society, Section on Pediatrics

President: Dr. K. J. Winters, 1411 Wauwatosa Ave., Milwaukee 13.
Secretary: Dr. Niels L. Low, 744 Main St., Racine.

## LOCAL

### Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. Charles H. York, 10465 Carnegie Ave., Cleveland 6.
Secretary: Dr. Earl E. Smith, 10640 Carnegie Ave., Cleveland 6.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

### Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St., W.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

### Baltimore City Medical Society, Pediatric Section

President: Dr. Wilson Grubb, 4 E. 33rd St., Baltimore 18.
Secretary: Dr. Gibson J. Wells, 3101 St. Paul St., Baltimore 18.

### Bronx Pediatric Society

President: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Secretary: Dr. George Weiss, 790 Grand Concourse, New York 51.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

### Brooklyn Academy of Pediatrics

President: Dr. Lewis A. Koch, 62 Pierrepont St.
Secretary: Dr. Stanley S. Lamm, 20 Plaza St., Brooklyn 17.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

### Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

### Central New York Pediatric Club

President: Dr. Frank Williams, 58 Swan Ave., Albany.
Secretary-Treasurer: Dr. Fred W. Bush, 26 S. Goodman St., Rochester.
Place: Various cities in New York. Time: Third Tuesday of April and October.

### Central Ohio Pediatric Society

President: Dr. E. V. Turner, 2479 E. Main St., Columbus.
Secretary-Treasurer: Dr. Mary L. Scholl, 1384 Grandview Ave., Columbus.
Place: As Announced. Time: Third Wednesday of September, November, January, March, and May.

### Chicago Pediatric Society

President: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka.
Secretary: Dr. Alfred S. Traisman, 6349 N. Clark St.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

### Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg.
Secretary: Dr. William F. Hunting, 6048 Montgomery.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

### Dade County Pediatric Society

President: Dr. William W. McKibben, 641 N. Greenway Drive, Coral Gables, Fla.
Secretary-Treasurer: Dr. Wesley S. Nock, 671 N.E. 57th St., Miami 38, Fla.
Time and Place: Variable.

### Dallas Pediatric Society

President: Dr. Fred Brooksaler, 4207 Lemmon Ave., Dallas.
Secretary-Treasurer: Dr. Charles L. Smith, 4207 Lemmon Ave., Dallas.
Place: Children's Hospital of Texas. Time: 6:30 p. m., the first Thursday of each month.

### Detroit Pediatric Society

President: Dr. Wilfred D. H. Nolting, 16840 E. Warren.
Secretary: Dr. Ruben Meyer, 938 Maccabees Bldg.
Place: Variable. Time: Five times annually.

### Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania.
Place: Welch and West Restaurant. Time: Third Friday of each month.

### Honolulu Pediatric Society

President: Dr. Walter B. Herter, 305 Royal Hawaiian Ave.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu 14.
Place: At doctors' homes in rotation. Third Thursday of each month, 6 p. m.

### Houston Pediatric Society

President: Dr. Byron P. York, 3911 Montrose Blvd.
Secretary: Dr. David Schrum, 3207 Montrose Blvd.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Tuesday of each month.

### Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway.
Place: Kansas City General Hospital. Time: On call.

### Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

### Long Beach Pediatrics Society

President: Dr. Lynn B. Vaughan, 302 Cherry Ave.
Secretary-Treasurer: Dr. Sam S. Woolington, 541 E. Broadway.

### Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1025 Wilshire Blvd. Time: Second Monday of February, April, June, October, and December.

### Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Irving S. Pearlman, 7602 Bay Parkway, Brooklyn.
Secretary: Dr. Irving Weinstock, 350 Ocean Ave., Brooklyn.
Place: Kings County Medical Society. Time: 8:45 p. m., fourth Monday of April, October, November, January, and March.

### Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2032 Belmont Rd. N. W.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E.
Place: Medical Society Bldg., 1718 M St. N. W. Time: Spring and fall.

### Memphis Pediatric Society

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

### Milwaukee Pediatric Society

President: Dr. A. L. Kastner, 1810 West Wisconsin Ave., Milwaukee 3.
Secretary-Treasurer: Dr. A. L. Babbitz, 606 West Wisconsin Ave., Milwaukee 3.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October, and December.

### Mobile Pediatric Society

President: Dr. Daniel Sullivan, 109 S. Broad St.
Secretary: Dr. Robert O. Harris, III, 1514 Government St.

### Nashville Pediatric Society

President: Dr. John M. Lee, Doctors Bldg., Nashville.
Secretary: Dr. Dan S. Sanders Jr., 2103 Hayes St.
Time: Third Thursday of every month.

### New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. Arthur F. Anderson, 122 E. 76th St.
Secretary: Dr. L. Emmett Holt Jr., 477 First Ave.
Place: New York Academy of Medicine, 2 E. 103rd St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

### Oklahoma City Pediatric Society

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

### Philadelphia Pediatric Society

President: Dr. T. F. McNair Scott, 1740 Bainbridge St., Philadelphia 46.
Secretary: Dr. F. H. Harvie, 133 S. 36th St., Philadelphia 4.
Place: College of Physicians, 19 S. 22nd St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

### Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708-15th Ave.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February, and April.

### Queens Pediatric Society

President: Dr. Meyerson Coe, 217-02 91st Ave., Queens Village, N. Y.
Secretary: Dr. Moe Goldstein, 111-32, 76th Ave., Forest Hills, N. Y.
Place: The Seminole Club, 112th St. and 70th Rd., Forest Hills, N. Y. Time: Second Tuesday in October, December, February, and April.

### Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

### Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

### St. Louis Pediatric Society

President: Dr. Donald L. Thurston, 500 S. Kingshighway, St. Louis 10.
Secretary-Treasurer: Dr. Leo F. Gowan, 337 W. Lockwood Ave., St. Louis 19.
Place: Candlelight House. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

### San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

### Santa Barbara Pediatric Society

President: Dr. Helen Hart, City Health Department, de la Guerra Plaza.
Vice President: Dr. Clarence Hills, 22B W. Micheltorena St.
Secretary-Treasurer: Dr. L. C. N. Wayland, 1235 Chapala St.
Meetings: Four times annually.

### Seattle Pediatric Society

President: Dr. David M. Harris, Medical Arts Bldg., Seattle 1.
Secretary: Dr. William A. Jaquette Jr., 1305 Seneca, Seattle 1.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

### University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

### Waco Pediatric Society

President: Dr. A. O. Manske, 1917 Austin Ave., Waco, Texas.
Secretary: Dr. M. C. Carlisle, 1410 Austin Ave.
Place: 1917 Austin Ave. Time: Third Tuesday of each month.

### Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).

### Western Michigan Pediatric Society

President: Dr. Horace L. French, 301 Seymour Ave., Lansing.
Secretary-Treasurer: Dr. John C. Montgomery, 1810 Wealthy St. S. E., Grand Rapids.
Time: Meets on the first Wednesday in October, November, April and May of each year. Two meetings are held in Grand Rapids and two in other designated localities.

### Wichita Pediatric Society

President: Dr. Walter L. Schafer, 401 N. Emporia St., Wichita 2, Kan.
Secretary: Dr. William F. McGuire, 401 N. Emporia St., Wichita 2, Kan.
Place: Variable: Time: First Thursday of each month.

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| *causes no rebound constipation* | ☑ | ☐ | ☐ |
| *not habit-forming* | ☑ | ☐ | ☐ |
| *does not interfere with vitamin absorption* | ☑ | ☐ | ☐ |
| *does not interfere with digestive process* | ☑ | ☐ | ☐ |
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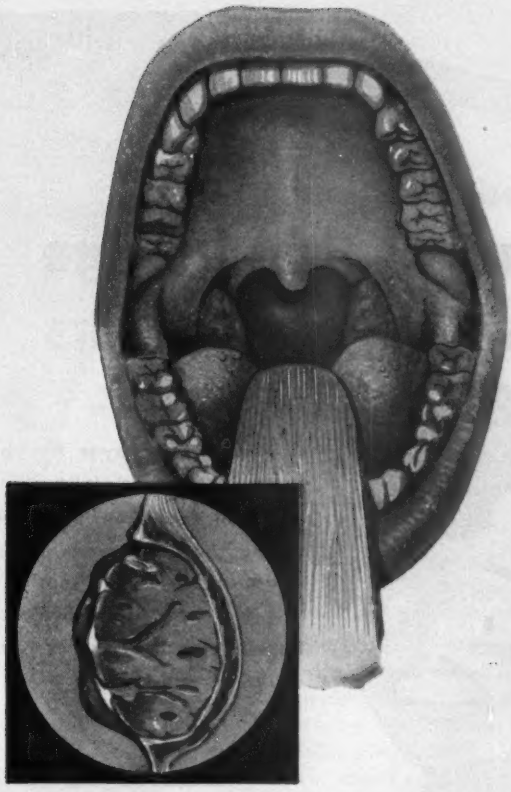

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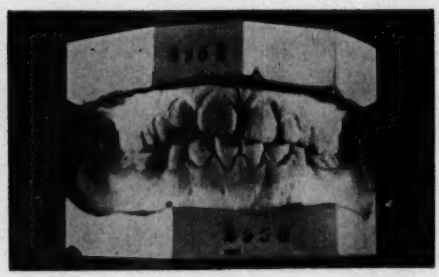

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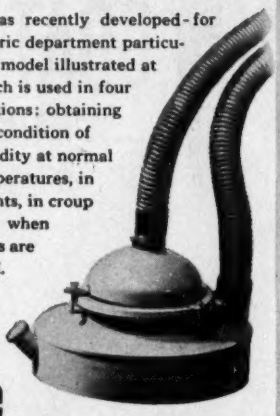

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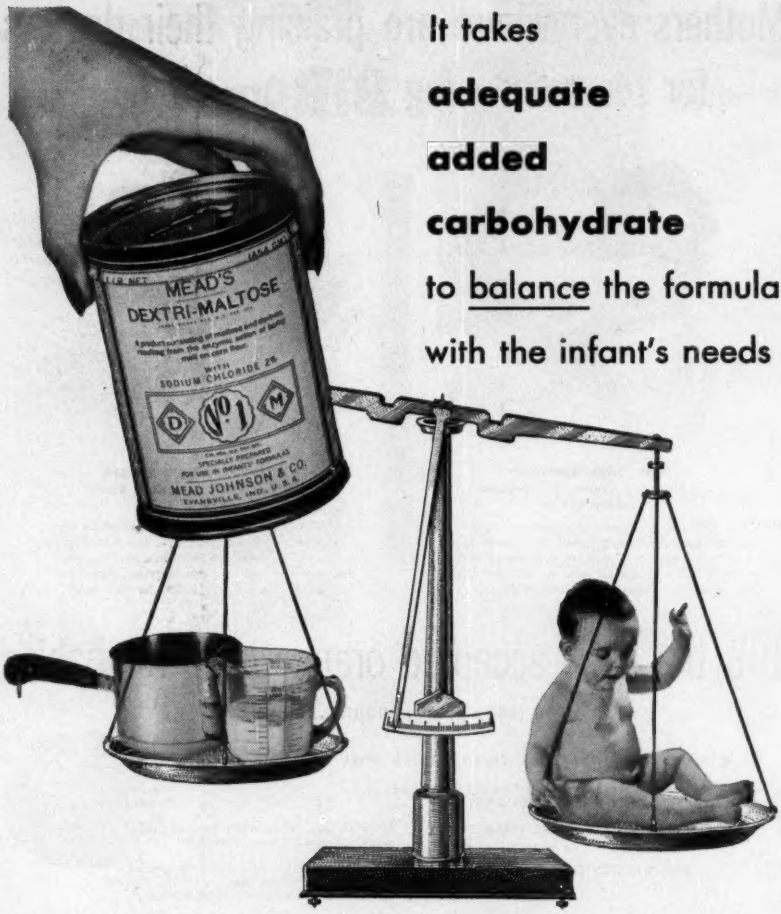
| **FLAVOR** . . . . . | Held constant by analysis of Brix-Acid ratio and addition of minimal amounts of dextrose. |
| **BACTERIA COUNT** . . . . . | Under 10/ml. (Fresh juice averages 25,000/ml., frozen averages 15,000/ml.) |
| **PULP CONTENT** . . . . . | BIB reduces fruit cells to microscopic size—retaining natural nutrients while assuring a juice free flowing even through bottle nipples. |

**Tell your mothers the BiB "6-Second" story**

**just open . . . pour . . . and feed!**

***P.S. Drop us a card and we'll send you full-size samples and literature. Write The BIB Corporation, Box 866, Dept. C9, Lakeland, Florida.***

**THE BIB CORPORATION • LAKELAND, FLORIDA**




# It takes **adequate added carbohydrate** to balance the formula with the infant's needs

Added carbohydrate is *required* for well balanced formulas. *Adequate* carbohydrate:

1. Spares protein for tissue building functions.
2. Permits proper metabolism of fat.
3. Promotes optimum weight gain.
4. Encourages normal water balance.

Pediatric authorities recommend a caloric distribution of about 15% from protein, 35% from fat, 50% from carbohydrate. For 40 years, cow's milk and Dextri-Maltose® formulas with this approximate caloric distribution have been used successfully.

These formulas very often consist of ⅓ evaporated milk, ⅔ water and 5% added Dextri-Maltose—about 1 level tablespoon Dextri-Maltose to 5 ounces of formula.

MEAD'S

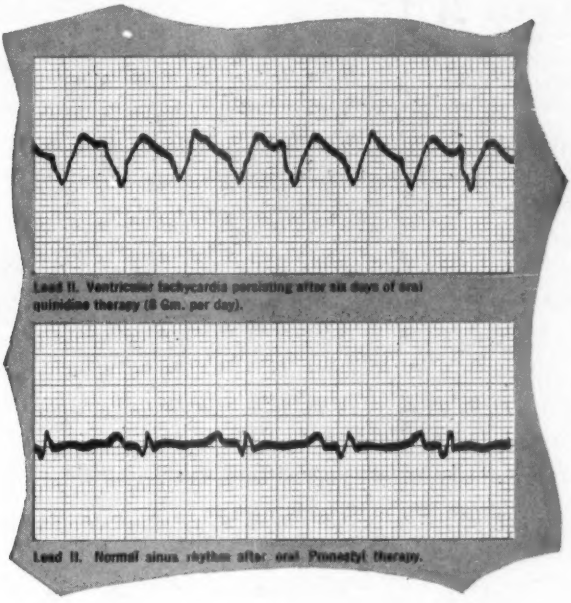
MEAD JOHNSON & CO.
EVANSVILLE 21, IND., U. S. A.

a new drug . . .

*for the treatment of ventricular arrhythmias*

# PRONESTYL *Hydrochloride*

***Squibb Procaine Amide Hydrochloride***



Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).

Lead II. Normal sinus rhythm after oral Pronestyl therapy.

**Oral administration of Pronestyl is indicated in ventricular tachycardia and runs of ventricular extrasystoles. Intravenous administration is sometimes used in ventricular tachycardia and to correct ventricular arrhythmias during anesthesia. For detailed information on dosage and administration, write for literature or ask your Squibb Professional Service Representative.**

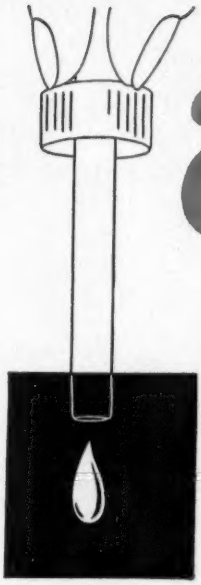
PRONESTYL IS A TRADEMARK OF E. R. SQUIBB & SONS

**Pronestyl Hydrochloride Capsules, 0.25 Gm., bottles of 100 and 1000.**
**Pronestyl Hydrochloride Solution, 100 mg. per cc., 10 cc. vials.**

**SQUIBB** MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

*Dispersible*
**DRISDOL®**
**WITH**
**VITAMIN A**

**COMPLETELY**
*Milk*
*Diffusible*



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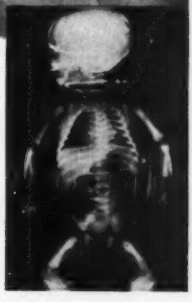

Drisdol with Vitamin A administered in milk becomes an integral part of the child's diet. It diffuses completely in milk, orange juice and other liquids without an oily film, does not separate, float or tend to adhere to nursing bottle or nipple. May also be given on the tongue or in solid foods.

Drisdol with Vitamin A contains per gram 50,000 units of vitamin A and 10,000 units of crystalline vitamin $D_2$ (calciferol). Each drop delivers 1250 vitamin A units and 250 vitamin D units.

**Dosage** for infants, 2 drops; for older children and adults, from 4 to 6 drops daily in milk.

Supplied in bottles of 10 cc. and 50 cc. with dropper.

Also Drisdol in Propylene Glycol (10,000 units of vitamin $D_2$ per gram) in bottles of 5 cc., 10 cc. and 50 cc.

*To help build a sound structure and promote growth*

Drisdol, trademark reg. U. S. & Canada, brand of crystalline vitamin $D_2$ (calciferol)

Winthrop-Stearns INC.
NEW YORK, N. Y. WINDSOR, ONT.